THE AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

DECEMBER, 1944

ORIGINAL ARTICLES

MYASTHENIA GRAVIS TREATED WITH LARGE DOSES OF NEOSTIGMINE METHYLSULFATE, INTRAMUSCULARLY AND INTRAVENOUSLY, AND WITH NEOSTIGMINE BROMIDE ORALLY*

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Since the discovery by Walker[11,12] of the efficiency of neostigmine (prostigmine) in the treatment of myasthenia gravis, the drug has been used extensively, both orally in the form of neostigmine bromide and parenterally as neostigmine methylsulfate. Most patients are maintained on oral medication, as first reported by Everts[2] and subsequently by Laurent and Walker,[5] Viets, Mitchell and Schwab,[10] and many others. Recently Viets[9] has emphasized the need in some cases for large oral doses up to 25 tablets in 24 hours (375 mg.), and reported upon one patient who had been maintained on this intake daily for more than 2 years without untoward effects. The use of neostigmine bromide in such large amounts greatly exceeded the dose of 45 mg.,[6,7] usually recommended, but Viets[9] found the average amount used by 45 patients in his clinic to be 163.5 mg. in 24 hours. No ill effects from taking these amounts over periods of years had been noted. The patients did not become tolerant to the drug, and, when spontaneous remissions in their symptoms of myasthenia gravis appeared, the patients were quickly able to reduce their maintenance intake, or, in some favorable cases, to omit the drug entirely for varying periods of time. That neostigmine is relatively less toxic than originally considered, especially by Goodman and Bruckner,[3] is now fully realized.

The amount of neostigmine methylsulfate, given parenterally, has also greatly exceeded the dose ordinarily used, although no reports have appeared in the medical literature on this aspect of the treatment of patients with myasthenia gravis. Such a case has recently been observed. The drug was used both intramuscularly and intravenously in large amounts.

Case Report. *History.* A. J. T., a married man of 68, American, was admitted to this hospital on May 21, 1943, because of progressive general

* The neostigmine was furnished by Hoffmann-La Roche, Inc.

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weakness, diplopia, dysphagia and dysarthria of 8 months' duration. His first symptom, in September, 1942, was diplopia; ptosis followed in January, 1943. By February he had difficulty in moving his shoulders, lifting his head off the bed and holding up his jaw. Swallowing weakness and nasal speech developed shortly. When attempting to swallow liquids, the fluid escaped through his nose. A test,[8] with the diagnostic ampule of neostigmine methylsulfate, was positive for myasthenia gravis, all symptoms of muscle weakness disappearing promptly. On oral medication of 6 to 10 tablets of neostigmine bromide, 15 mg. each, spaced at intervals of 2 to 3 hours during the day, the patient was considerably improved. He began soon, however, to relapse. To counteract his increasing symptoms, his intake of neostigmine bromide was raised to 16 tablets a day, augmented by intramuscular injections of neostigmine methylsulfate, 1 mg. each, 6 times a day. His average dosage before entering the hospital was 2 tablets of neostigmine bromide every 2 hours during the daytime, and every 3 hours at night. With each dose he took 4 drops of tincture of belladonna to prevent a diarrhea which occurred without it, using about 44 drops in each 24 hours. He swallowed only liquids with difficulty, being unable to take any solid food. A loss of 20 pounds in weight had occurred during the past 6 months. The response to the above dosage was irregular. The disease progressed slowly by relapses and mild remissions, with a general downward course. Up to a week before admission the patient was able to walk with only moderate weakness. During the following week he collapsed rapidly. Except for the symptoms noted above, the patient had few complaints. There was some dyspnea on exertion, a tendency towards mucus formation in his throat with an annoying cough and moderate urgency and frequency of urination. His mood was one of coöperativeness, without undue depression.

Past History. The patient had served as a missionary in India from 1901 to 1940, where he had several attacks of malaria. His last chill occurred in July, 1942, this attack being relieved by quinine, as in the past. There was also a history during his years in India of frequent intestinal upsets, with mild to severe diarrhea. Peptic ulcers were relieved by diet, without operation, in 1936.

Some dribbling at the end of urination had been noted for 10 years, with considerable frequency in the last few years. In October, 1941, obstruction to urination occurred. The prostate gland was removed by perineal prostatectomy at the Massachusetts General Hospital in November, 1941, and a papillary tumor from the bladder by transurethral resection in July, 1942, both operations taking place before the onset of his present symptoms of myasthenia gravis. Pathologic examination of the tumor showed it to be a carcinoma, Grade 2A.

Physical Examination. On admission, May 21, 1943, the patient was gravely ill. His eyes were fixed in about the midline, with moderate ptosis. The jaw hung partly open and the facial muscles were nearly immobile. His head could not be raised from the bed. Speech was thick, but understandable; his tongue could only be protruded to the line of the teeth. The arms could not be lifted above the level of the shoulders. The patient could move his legs, but could not turn over in bed. Swallowing was limited to small amounts of liquids. Choking spells occurred a number of times each day, often with shallow, diaphragmatic, gasping respiration. His throat was nearly constantly filled with thick mucus.

The patient's heart was slightly enlarged and the sounds were of poor quality. The blood pressure was 140 systolic, 100 diastolic. The general physical examination was otherwise not remarkable, except for coarse râles throughout both lungs.

Laboratory Reports. The specific gravity of the urine was normal; occasionally a trace of albumin was present, with a rare hyaline or granular cast. The hemoglobin was 15.3 gm. per 100 cc. The W.B.C. count was 4900 per c.mm., the differential count being within the limits of normal. The R.B.C. and platelets appeared normal; no malarial parasites were seen. The stool showed no blood, parasites or ova. Lumbar puncture was not done.

Treatment. On entrance to the hospital it was impossible for the patient to swallow neostigmine bromide by mouth and parenteral medication was begun (Fig. 1). At first 1 mg. of neostigmine methylsulfate was injected intramuscularly every 2 or 3 hours. As this dosage was insufficient to prevent attacks of dyspnea, the dosage was gradually increased to hourly injections throughout the 24 hours of 1 mg. or 1.5 mg. each. On one day he received

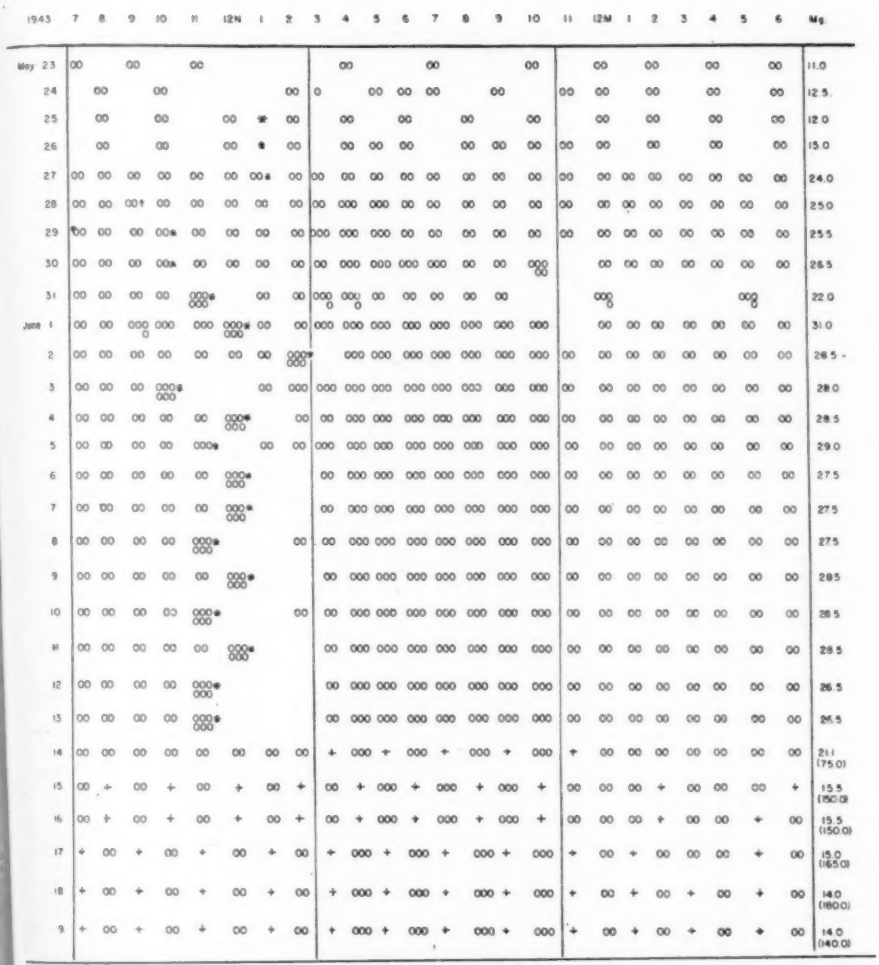

FIG. 1.—The hourly intake of neostigmine methylsulfate and neostigmine bromide in a severe case of myasthenia gravis during the first 3 weeks of treatment. The chart is divided into 3, 8-hour daily periods, according to the nursing schedule. 0 = neostigmine methysulfate, 0.5 mg. (1–2000). + = neostigmine bromide, 15 mg. An asterisk denotes intravenous medication. The total intake in milligrams of each drug is given in the right-hand column, the amount of the neostigmine bromide being in parenthesis.

31 mg. of neostigmine methylsulfate. Three mg. of this total each day was given intravenously in 1500 cc. of glucose solution to which it was added. The 5% glucose solution was also reinforced by 100 mg. of vitamin C, 10 mg. of thiamine chloride, 100 mg. of nicotinamide and 10 mg. of riboflavin. The formula of intravenous medication was slightly changed from time to time, but remained relatively constant for 3 weeks; the rate of flow was about 70

drops per minute. No difficulties were encountered in using this daily intravenous therapy.

The patient became well adjusted to his schedule of neostigmine in about a week and was maintained on 26.5 mg. to 29 mg. of neostigmine methylsulfate every 24 hours for the next 2 weeks. He showed no acquired tolerance to

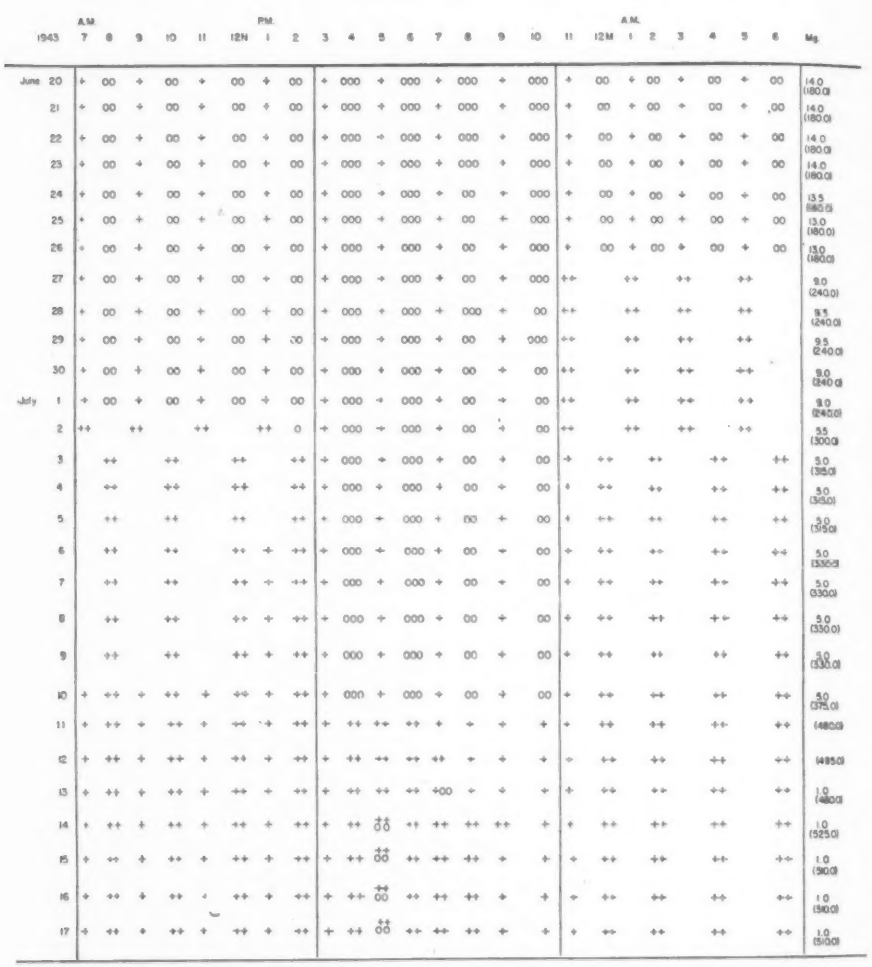

FIG. 2.—The hourly intake of neostigmine methylsulfate and neostigmine bromide in a severe case of myasthenia gravis during the second 3 weeks of treatment. For an explanation of the symbols used, see the legend under Figure 1.

the drug and intestinal stimulation was minimal. There were few cramps, but he had only 2 to 4 soft bowel movements each day without diarrhea. Atropine sulfate, 0.6 mg., was given only 5 times in 8 weeks. On the other days a few drops of tincture of belladonna was used. As his general condition slowly improved, swallowing became possible. Three weeks after entrance to the hospital (Fig. 1) the intravenous medication was stopped and administration of neostigmine bromide orally was slowly substituted for some of the intramuscular and intravenous injections (Fig. 2). Over a period of the next 5

weeks, treatment by mouth was gradually extended, until at the end of 8 weeks the patient was maintained on oral neostigmine bromide, as he had been 3 months before entering the hospital (Fig. 3). Ephedrine sulfate, 24 mg.,

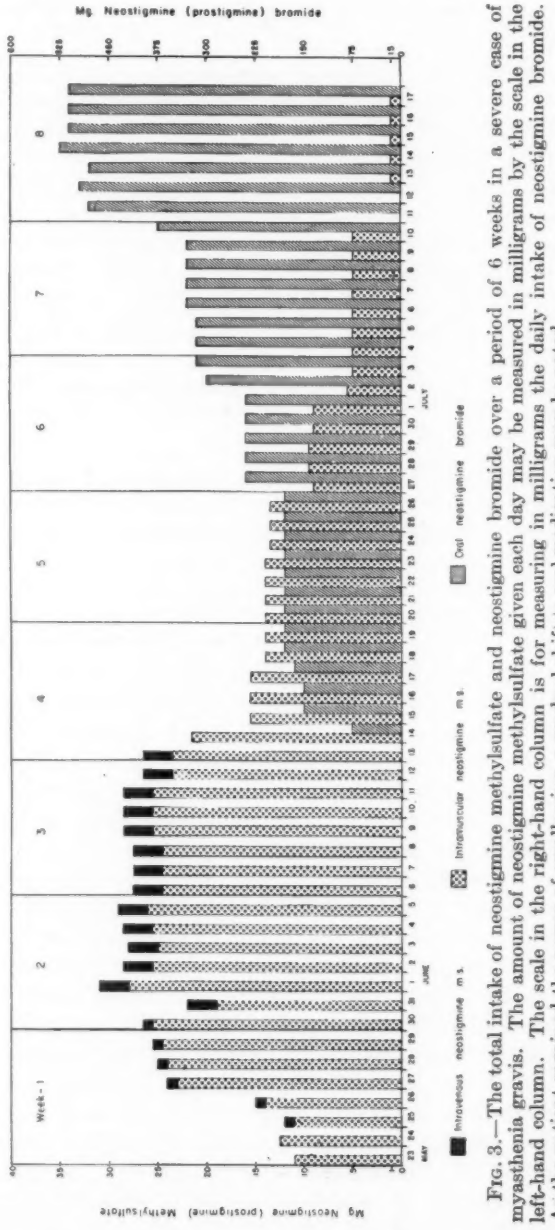

FIG. 3.—The total intake of neostigmine methylsulfate and neostigmine bromide over a period of 6 weeks in a severe case of myasthenia gravis. The amount of neostigmine methylsulfate given each day may be measured in milligrams by the scale in the left-hand column. The scale in the right-hand column is for measuring in milligrams the daily intake of neostigmine bromide. As the patient regained the power of swallowing, a gradual shift to oral medication may be noted.

1 tablet, crushed in water, 4 times a day, was used for about 4 weeks, but was discontinued because of restlessness and insomnia. Otherwise the only medication for myasthenia gravis used was neostigmine. Tincture of digitalis,

10 drops in water, once a day, was given throughout the patient's stay of 8 weeks in the hospital. On 2 occasions, when cardiac failure threatened, 4 cc. (0.8 mg.) of cedilamide was given and on another, 1.5 cc. of coramine, intravenously.

Nursing and Feeding. Of most importance was the constant nursing care; 3 nurses, each on 8-hour duty were employed to ensure constant observation. Thick, tenacious mucus was removed from the mouth and throat by suction or by postural drainage. The hourly medications required much of the nurses' time. The opening of 60 or more ampules a day was a task, finally obviated when neostigmine methylsulfate was procured in ampules of 10 cc., each containing 5 mg.*

During the first week of hospitalization the patient was only able to swallow a small amount of liquid. On some days 500 to 1000 calories of food could be given by mouth; this was supplemented by 200 to 400 calories of glucose, intravenously. Because of the danger inherent, when dysphagia is present, to intubation in myasthenia gravis, tube-feeding was not resorted to. As the patient slowly improved, due to better adjustment of his intake of neostigmine methylsulfate, his total calorie intake during the second week was raised to a level of 1000 calories a day. Gradually this was pushed up to a level of over 2000 calories before the patient left the hospital at the end of 8 weeks. Most of the food consisted of milk, cream, puréed vegetables, eggs, finely ground-up meat, and bread. On the day he left the hospital, July 30, 1943, about 2400 calories were taken by mouth.

Subsequent Course. The patient did not do well at home. Special nursing could not be provided and adequate medical supervision was not available. He died of respiratory failure, or possibly of cardiac complications, August 6, 1943, a week after discharge. Postmortem examination was not allowed.

Discussion. The use of neostigmine in the treatment of myasthenia gravis is based upon the following assumptions: (1) acetylcholine is a necessary ingredient in the complex chemical status that permits the passage of an impulse from nerve to muscle; (2) cholinesterase is the enzyme concerned with the destruction of acetylcholine by hydrolysis; (3) in myasthenia gravis there is an abnormal reaction at the myoneural junction between acetylcholine and cholinesterase; (4) neostigmine is a potent inhibitor of cholinesterase activity, combining loosely with it; (5) when neostigmine is dialyzed off from cholinesterase *in vitro*, restoration of full enzymatic activity results; (6) probably a similar chemical reaction takes place *in vivo*, unless a sufficient supply of neostigmine is continuously at hand to inhibit cholinesterase activity.

Thus the therapeutic aim in the treatment of myasthenia gravis is to supply enough neostigmine to a patient to offset the activity of the cholinesterase, resulting in an excessive or too rapid destruction of the acetylcholine. Cholinesterase may be found along the nerve pathways, at the level of the nerve cells in the central nervous system and at the myoneural junction. In myasthenia gravis, the main focal point of imbalance appears to be at the myoneural junction, but other points may also be involved. With our present knowledge, a chemical imbalance at the myoneural junction accounts best for the main symptom of the disease, namely excessive fatigue of muscular response to voluntary nerve stimulation.

* These special ampules were provided by Hoffmann-La Roche, Inc., for the purpose of clinical research.

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When oral treatment is given, using prostigmine bromide, there are many factors that tend to prevent a continuous and even supply reaching the myoneural junction of the affected muscles. In order to maintain the highest and steadiest level of neostigmine at the focal point, the drug is given in spaced doses during the day and night; larger doses are used at times of greatest fatigue, as in the afternoon period and during mealtime. Too rapid removal from the stomach is avoided by an ingestion of some food with each oral medication, or the drug may be absorbed sublingually. Parenteral treatment may be used to augment the oral intake in times of excessive need. Thus a carefully planned, schedule dosage is sufficient control for the maintenance of the average case of myasthenia gravis. The uncontrolled factors, such as the failure to assimilate the drug, its loss in other areas of the body than the specific myoneural junctions involved and the destruction and elimination of neostigmine without absorption, a matter not fully understood, are not of great clinical importance in the treatment of most cases. Such unknowns can be offset by increased dosage and large doses do not appear to affect most patients adversely.

With the use of neostigmine parenterally, the problem becomes less complex, for the uncertainty of absorption *via* the gastro-intestinal tract in oral medication, is eliminated. The principle of treatment remains unchanged. Maintenance is established at an adequate level, although, as indicated in the case abstract, the level may exceed our preconceived ideas in regard to toxicity and tolerance. When the patient, reported upon, was doing badly, in the first few days of his hospitalization, it was soon discovered that underdosage and not overdosage was the fault. The daily intake of 11 mg. was raised to nearly 3 times that amount and the patient became well adjusted and nearly symptom free. At the proper time, moreover, when he was fully maintained and improved, the amount of the drug was reduced without ill effect and oral medication was substituted. No tolerance developed. This has been found to be so in most cases of myasthenia gravis treated by the author. What is usually called "developing a tolerance to the drug" is merely an acknowledgment of inadequate dosage.

The intravenous use of neostigmine methylsulfate was first tried in this case. It was found that the drug was well tolerated, that it could be added to glucose solution and other forms of medication could be used in the same intravenous preparation. When given over a period of hours, the same amount could be used as was given intramuscularly. Using the drip method, 1.5 mg. could be given in 1 hour. Subsequently, in other patients this dose has been doubled, without ill effects. The possibility of using neostigmine intravenously opens up a new field for emergency treatment and, since experience with this patient, the drug has been frequently used for this purpose. No difficulties have been encountered. On the basis of experiments with the related drug, physostigmine,[4] neostigmine has been given by continuous intravenous infusion in myasthenic patients in the Department of Surgery at the Massachusetts General Hospital.[4] By this means the neostigmine needs of the individual patient were assayed preoperatively and appro-

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priate levels of cholinesterase inhibition were maintained during and after thymectomy.

The signs in man of a fatal dosage of neostigmine are uncertain. No patient is known to have died of the drug. When patients are taking more neostigmine than is needed to inhibit the cholinesterase, muscular fibrillations or fasciculations will appear as evidence of cholinergic overstimulation of the muscular skeletal system. In addition, salivation, a lowering of the heart rate and a stimulation of peristaltic activity, with or without cramps, will be noted. These are the signs that occur when the drug is given to a normal person,[3] and they are seen in cases of myasthenia gravis if more neostigmine is given than is needed. When large doses are used, these signs should be watched for. In our experience, the most important early sign is the fibrillation or fasciculation of the facial muscles. The symptoms of overdosage usually respond to atropine sulfate.

Summary. 1. Patients with severe myasthenia gravis may be maintained on neostigmine methylsulfate, intramuscularly, spaced at hourly intervals, in doses up to 31 mg. per 24 hours.

2. The drug may also be given intravenously, in doses as high as 3 mg. per hour, by the continuous drip method.

3. Neostigmine and other drugs can be safely added to the intravenous glucose solution.

4. Tolerance for neostigmine was not shown in the doses used.

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PURULENT MENINGOCOCCAL ARTHRITIS

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Arthralgia and myalgia are common complaints at the onset of many of the acute febrile diseases and meningococcal infections are not exceptions in this regard. Most authors on the subject of meningo-

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coccal infections mention the frequency with which joint and muscle pains occur but few give any particulars concerning the joint manifestations. When arthritis is referred to it is usually described as accompanying the rash and disappearing with the rash without any treatment being needed and without leaving any sequelæ. Indeed, this form of arthritis has been regarded as so mild that little notice has been given to it. Apart from this transient form of arthritis purulent meningococcal arthritis occasionally occurs.

At the present time, when sulfonamide drugs are so effectively being used in the treatment of meningococcal infections, the septicemic stage of the disease is readily controlled, so that we may expect to see fewer of the metastatic manifestations than ever before. But it is of interest that, even before the day of sulfonamides, arthritic manifestations of meningococcal infections had been noted; but, nevertheless, there have been few reports of purulent meningococcal arthritis. The first observers of "spotted fever" have given us excellent clinical descriptions of the disease, and their remarks about arthritis are pertinent. North and Swords[22] called attention to the "rheumatism" in connection with cerebrospinal fever, and Welch, Jackson and Warren[41] said: "In some cases swellings have occurred in the joints and limbs. These have been very sore to the touch and their appearance has been compared to that of gout. The parts feel as if they had been bruised. These swellings are in the smaller as well as the larger joints and are often of a purple color. Those of the small joints especially soon disappear as the disease approaches its crisis." This description was made before the discovery of the meningococcus as the cause of "spotted fever" and it very nicely dovetails with the word-picture given to us by Herrick and Parkhurst[12] at a later date.

von Fronz,[38] in 1897, first isolated the meningococcus from fluid drawn from a joint and should be credited with the first case of proven meningococcal arthritis. In 1899, Gwyn,[8] working on Osler's service at Johns Hopkins Hospital, isolated the meningococcus from the blood, "joint fluid and cerebrospinal fluid of a case which Osler described as illustrating probably the maximum degree of involvement of the joints in cerebrospinal fever." There was "swelling and redness of both elbows, the right wrist, the right knee, and several of the smaller joints of the hands."

It was the violence of the polyarthritis noted in the case here reported that attracted our attention to the subject of meningococcal arthritis, and we believe that it also represents "the maximum degree of involvement of the joints in cerebrospinal fever."

Case Reports. CASE 1. E. D. E. (A18900), age 52, white, widowed. This saleswoman was in her usual good health until February, 1943, when she suffered from a "cold" with cough, sore throat, and aching all over. Her physician prescribed white pills to be taken ever 4 hours (not sulfonamide medication). After a week in bed and several days spent about the house, the patient felt sufficiently well to return to her work, but felt only "fairly well," for she still had chilly sensations and muscular aching.

January 10, 1943: Sore throat, malaise, headache, general muscular aching and nausea were noted; the same physician prescribed the same tablets once

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again. Only 3 doses of the medicine had been taken when nausea and vomiting began. General aching became more severe, joint pains were complained of, and finally chills began. These chills were "shaking chills" and after the first one "spots" appeared on the hands, feet, forearms and lower legs. The patient ascribed her nausea to the medication and took only 7 tablets in all. The repeated chills, high fever, headache and exquisitely tender joints finally forced the patient to come to the hospital.

January 15, 1943: The patient was acutely ill and complained bitterly of the pain in "every joint;" she was mentally clear but was in such pain that both the history and examination were abbreviated. Temperature was 103° F., pulse 110, and respirations 25, blood pressure 150/70. The skin presented a fine, purpuric rash over the ankles and lower thirds of both legs, and in addition several petechiæ on the thighs and abdomen. Also, there were scattered over both hands, forearms and feet several larger purpuric spots which measured from 3 to 10 mm. in diameter. None of these "spots" blanched on pressure, and several of the larger ones were indurated and tender; the likeness to erythema nodosum was noted. The thorax, back and abdomen showed only a few scattered petechiæ.

The eyes presented a purulent discharge which was crusted on the eyelashes and eyelids so as to almost glue the lids together. The corneæ were clear and there were no ulcerations.

The chest was clear, the heart regular and apparently normal, and the abdomen soft. A special effort was made to feel the spleen, but it could not be palpated.

All joints were exceedingly painful, the patient refused to make any effort to move them and the slightest passive movement caused pain. Both hands looked frankly edematous, the dorsum of each being swollen and tense. The resemblance to the infections of the hand was striking. There was a splotch of purple discoloration over each of the metacarpophalangeal joints and the dull-red of inflammation about both wrists; the wrists were swollen, the right more than the left, and the patient would tolerate no movements of either hand. Both elbows were tender, swollen and red, and held in semiflexion across the abdomen. Due to the pain in the lower arms, the shoulders could not be properly evaluated, tenderness on palpation was elicited but there was no swelling and no redness. The neck was supple, the temporomandibular joint normal, and the chest gave no pain on forced inspiration and expiration. Both feet were swollen and both ankles were red, hot and tender; movement of the toes was painful. The left ankle joint was larger than the right, but both presented evidence of effusion into the joints. Both knees were swollen, hot, red and tender and fluid was present in both joints. Movements of the hips were not tested.

The arthritis in this case was the most striking feature and, in view of the ophthalmia, the joint symptoms, and a rather indefinite social history, the diagnosis of gonococcemia and gonococcal arthritis was entertained. The patient vigorously denied exposure, urethral and cervical smears were negative for gram-negative diplococci, and an unsatisfactory pelvic examination showed showed nothing abnormal.

Meningococcemia was suspected, although none of us had ever seen such an outspoken and acute arthritis in this condition. Lumbar puncture yielded clear spinal fluid under normal pressure, the cell count was normal, no organisms were demonstrated on smear, and culture of this fluid was later reported as negative.

The purpuric nature of the skin rash, together with knowledge of previous medication, suggested a blood dyscrasia. Tests of capillary fragility gave normal results, bleeding time 2 minutes 5 seconds, clotting time 4 minutes, prothrombin time (Quick) 16 seconds, clot retraction at the end of 1 hour, platelet count 429,000 per c.mm. were all normal values.

The fulminating nature of the arthritis and the fine rash chiefly on the lower extremities caused us to think of Haverhill fever. Dr. L. E. Sutton[25] saw this

case in consultation and agreed that the clinical appearance of this patient was such as to justify the consideration of this diagnosis.

Aspiration of the left knee was done and approximately 50 cc. of thick, yellow pus was obtained; a smear of this pus revealed countless numbers of both intracellular and extracellular gram-negative diplococci. Fluid was obviously present in both ankles, certainly in the right wrist, and probably in several of the metacarpophalangeal joints, but it was deemed unwise to tap these joints for purely academic reasons.

The patient was given 6 gm. of sodium sulfadiazine intravenously and 1 gm. orally every 4 hours thereafter. Morphine was given without stint for the relief of joint pain, and splints were applied to the left leg, the right leg, and the right wrist. These measures made the patient fairly comfortable.

As late as the 5th hospital day it was the general feeling that this woman suffered from gonococcemia and gonococcal arthritis; this feeling had been strengthened by the reporting of a positive gonococcal complement-fixation test. But at this time both the blood culture and the culture made from the joint fluid were reported as showing growths of meningococci. The organism was typed as a Type I meningococcus by the National Institute of Health. The gonococcal complement-fixation test was repeated and found positive on 2 more occasions.

The fever subsided by lysis, the joints became progressively less tender and swollen, and the rash rapidly faded. The larger purpuric spots left brownish discolorations and some of the "erythema-nodosum-like" lesions during their period of regression took on the appearance of bruises with all of the attendant color changes.

Sulfadiazine therapy was given for 19 days at which time the patient had a total white count of 3200 and was running a mild fever; the drug was discontinued. Most of the joints had become non-painful, but the left knee was still swollen, and the right hand was still definitely swollen. The knee could be flexed beyond 90 degrees but it felt "stiff." Grasp with the right hand was poor and the wrist could not be dorsiflexed.

February 21, 1943 (30th hospital day): Without apparent cause the patient became fretful, recalcitrant, resisted the medical attendants and talked foolishly. During the following days the patient became actively hallucinated, expressed fears that the nurses and doctors were poisoning her, and became unmanageable on an open Medical Ward. On the 49th hospital day this woman was discharged in the care of her family. There is no explanation for this psychosis.

Follow-up of this patient revealed that on the 80th day from the onset of her arthritis the left knee still ached, the left ankle swelled after walking, the right hand remained swollen. Roentgen ray of the right wrist revealed "destruction and narrowing of the joint space due to infectious arthritis."

Case 2. Miss L. B., age 24 years, white, single. This case-worker had for several months been employed in social work and had been visiting in numerous homes. While visiting her sister, she was taken ill with a "cold," headache, muscle soreness and a rash. The sister, a student nurse, put the patient to bed and went off to attend a lecture, the subject of which was "Meningococcemia and Meningococcal Arthritis," which was being presented by the author before the Staff of the Medical College of Virginia. Returning from the lecture, this observant student nurse had her sister admitted to the hospital at once with the presumptive diagnosis of meningococcal infection, and the author was called to see the case.

The patient was alert and somewhat bewildered that she should be so precipitously admitted to the hospital. Examination revealed a temperature of 102° F., pulse 100, respirations 24. The patient was comfortable, complained of slight soreness of the muscles generally, slight headache and some slight nausea. The neck was slightly painful on anterior flexion, Kernig's sign was negative bilaterally, and the reflexes were physiologic. The skin presented a hemorrhagic rash limited to the arms and legs, both palms and soles presented spots ranging from 5 to 10 mm. in diameter. The chest was clear, the heart normal in size, rhythm and sounds, the abdomen was soft, and the spleen

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could not be felt. A lumbar puncture was done and slightly cloudy fluid was obtained that revealed 500 cells per c.mm.; organisms were not seen on smear but culture of this fluid was positive for meningococci. A blood culture taken at this time was noted to be positive for meningococci.

The joints were carefully examined and the left knee was found to be slightly swollen. The patient herself had not been aware of this fact and there was no pain on manipulation of the joint, flexion was slightly limited by a feeling of "fullness." There was no redness or tenderness of this joint. Aspiration was done and thick, yellowish fluid was obtained which on smear revealed gram-negative diplococci. Culture of this fluid was positive for meningococci.

The patient was given 3 gm. of sulfadiazine as an initial dose and 1 gm. every 4 hours to a total of 25 gm. Recovery was entirely uneventful, no special treatment was given to the knee, and normal function was restored. Follow-up 1 year later revealed that there had been no disability with regard to the left knee.

Discussion. It is difficult to know the exact incidence of meningococcal arthritis, for many authors either do not mention it at all or mention it so slightingly that one wonders whether they refer merely to arthralgia or to true arthritis. When arthritis is specified, it is frequently stated that it is transitory, disappears with the rash which accompanies it, and does not present the local signs of inflammation.[5,19,27,30] The statement is made almost universally that meningococcal arthritis is "self-limited," that little or no treatment is necessary, and that restoration of joint function is complete. It is small wonder that little attention has been paid to meningococcal arthritis.

Herrick and Parkhurst[12] collected the largest single series of cases of meningococcal arthritis and classified the different forms that the disease might take. Their Type C was merely the arthritis of serum sickness and needs no further comment. Of Type A they said, "Almost all these cases have profuse hemorrhagic rashes coincident with the polyarthritis. In many but not in all instances, the arthritis is transitory as the rash. It would seem that these early joint symptoms are due to hemorrhage into the articular and periarticular structures, especially the synovia, and are identical with the hemorrhagic lesions of the skin and serous membranes." Bauer and Short[1] similarly explain arthritis as "hemorrhage into the joints," but it is of interest to note that Herrick and Parkhurst[12] clearly stated that aspiration was not done in any of these cases, so that no evidence is offered as proof of "hemorrhage into the joints." However, Keefer *et al.*[17] studied several joints pathologically and demonstrated acute inflammatory changes and gram-negative diplococci in the deep layers of the synovia, but an intact synovial surface layer, thus establishing the fact that the process may be purely a "synovitis." These authors concluded, "Meningococcic arthritis is a metastatic lesion involving first the deeper synovial tissues. Later, infection invades the superficial cells with effusion of fluid into the joint cavity and varying degrees of destruction of the cartilage. It is essentially a metastatic acute synovitis."

Thus the Type A arthritis of Herrick and Parkhurst can be designated as an acute synovitis. As the result of extension of the synovitis, Type B arthritis may result. "With few exceptions only one joint is

affected, generally the knee, occasionally the ankle, hip, shoulder, wrist or elbow. . . . . Effusion is a prominent feature so that aspiration of the synovial capsule is suggested in many cases. Swelling is great, but redness, pain, tenderness and limitation of motion are surprisingly slight. Often a tensely swollen joint can be manipulated freely, with only moderate discomfort. In no other acute arthritis is there this striking disproportion between the swelling and the other inflammatory signs. . . . . The duration of the process is usually from 1 to 4 weeks, recovery being gradual but complete. Rarely stiffness and slight pain or muscular spasm remain for a long time."

TABLE 1.—REPORTED CASES OF MENINGOCOCCAL ARTHRITIS

Reference	No. of cases meningococcus infection	No. of cases with joint effusions specifically	Cases with "arthritis" (%)
Rogers*	Not stated	Not stated	20.0
Osler*	21	Not stated	9.5
Councilman, Mallory, Wright*	111	Not stated	5.4
Sophian[32]	Not stated	Not stated	10–15
Rolleston and Andrewes[29]	1773	Not stated	5.3†
Hodes and Strong[13]	110	Not stated	4.5
Rundlett, Gnassi, Price[30]	17	Not stated	41.0
Stone, Truitt[34]	215	1	24.0
Herrick[11]	315	Not stated	10.0
Stott, Copeman[33]	17	3	17.6
Harries[9]	500	Not stated	5.4
Joe[15]	500	Not stated	4.2
Lepper, Sweet, Dowling[20]	121	Not stated	2.4
Thomas[27]	1935	Not stated	"a few"
Waghelstein[29]	580	Not stated	2.7
Tillett, Brown[36]	26	Not stated	43.0
Boger, Robertson‡	125	2	3.6

* Cited by Herrick and Parkhurst.[12]
† Synovitis.
‡ Unpublished data.

Certainly this type of joint disease deserves the name of "purulent arthritis," and it is to this type of meningococcal arthritis that we wish to direct attention. Case 2 beautifully illustrates the painlessness and the absence of local manifestations of inflammation in this type of joint involvement.

Case 1 stands in sharp contrast to Case 2. It seems likely that the patient had been ill for a month or more and that her recurrent muscle aches and chilly sensations were due to a chronic meningococcemia. At the time of hospitalization the meningococcal septicemia was at its height, with the production of a marked purpuric rash and a very acute polyarthritis; the coincidence of these two manifestations must be stressed. This polyarthritis was probably due to acute synovitis, and most of the lesions producing the joint manifestations resolved in a short time; but a number of the joints at this time were noted to have frank effusions in them. The evolution of this case shows rather clearly the relationship of Type A and Type B arthritis, the latter being merely an extension of the former, and the clinical observations in this case coincide exactly with the pathologic studies of Keefer *et al.*[17]

The coincidence of the rash and arthritis has been repeatedly noted, and those cases of chronic meningococcemia in which recurrent septi-

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cemia with the production of chills and fever, rash and arthritis permits repeated observations of the same sequence of events, seem to establish a close relationship between the two phenomena. There seems little reason to doubt that the synovial linings of joints present a "rash" just as the skin does, with resultant arthritic symptoms, but it still seems unnecessary to postulate hemorrhages into the joints. On the skin the meningococcal rash may present macules, petechiæ, intracutaneous hemorrhages and erythema nodosum-like lesions; and if one grants the same variability of the rash on the synovial surfaces, one can readily understand pain, tenderness, redness and "arthritis as transient as the rash which accompanies it,"[12,41] without postulating hemorrhage into the joint.

If we regard the profuseness of the skin rash as a possible indication of a similarly profuse involvement of synovial surface, it becomes merely a quantitative relationship between profuseness of the rash and the extent of the synovial lining of a particular joint, which determines the frequency with which the joint is involved by a purulent effusion. The larger the extent of the synovial lining of a particular joint the more likely it is that one or more of the septic metastases will extend into the joint. This seems to be compatible with the finding that the larger joints, and particularly the knee, are most often involved by suppurative meningococcal arthritis.

Despite the commonness of meningococcal infections and the naming of the disease "spotted fever" because of the commonness of the rash, purulent meningococcal arthritis is a relatively rare disease. Table 1 presents some scattered statistics on the incidence of arthritis in the presence of meningitis, but none of the authors cited presents bacteriologic proof of any case of arthritis noted. Herrick and Parkhurst[12] collected 16 cases of Type B arthritis; only 8 were aspirated and in only 4 was the meningococcus isolated. Schein[3] found 23 cases of "meningococcal arthritis" during a 10-year period, but only 4 of these cases were established bacteriologically. Kobayoshi,[18] Gwyn,[8] Jaffe[14] each proved 1 case by isolation of the meningococcus from joint fluid. Dock,[6] in reviewing 68 cases of meningococcemia, mentions 3 joint effusions but gives no bibliography. Rolleston[28] mentions aspiration of a joint, but no culture was obtained; similarly, Stott and Copeman[35] encountered 3 joint effusions, but no aspirations were done. Moss[21] reported 1 case with bilateral effusions of the knees and another case with a joint effusion, but cultures were sterile. Although we have not reviewed the literature exhaustively, it seems plain that the isolation of meningococci from the joints is uncommon.

In the light of the close relationship between the rash and arthritis, and the fact that both are manifestations of septicemia, the demonstration of meningococci in the blood or cerebrospinal fluid might appear to be proof of etiology of the joint manifestations. While such evidence is probably acceptable we believe that anything short of the demonstration of meningococcus from the joint involved leaves the case open to question. Cattell[3a] calling attention to the rarity of meningococcal arthritis, nevertheless fails to present bacteriologic

proof of his case. It may seem overcritical to stress this point, but Curtis[4] described a case which presented a clinical picture identical with Case 1, and yet the *Micrococcus catarrhalis* was isolated from the joints. Pharyngeal Neisseria occasionally cause meningitis, and unless careful bacteriologic study is made, these organisms may be often called meningococci. Sophian[33] cites a case of his own and calls attention to the literature on this point. Thus it seems best to establish the diagnosis of purulent meningococcal arthritis on bacteriologic grounds rather than clinical circumstantial evidence.

It is interesting to review the prognosis of the few cases of proven meningococcal arthritis. The prognosis of the acute synovitis is uniformly excellent, but when the joint space is involved the prognosis should be a little more guarded. In the series of 16 cases reported by Herrick and Parkhurst,[12] there were 2 deaths and a flexion deformity of the knee. These authors also mention 1 case of "necrosis of the head of the radius" following meningococcus arthritis of the wrist. Of Schein's[31] 23 cases, only 4 were proven by culture; but of these 4, 2 had ankylosis of the joints and the other 2 had limitation of function of the joints. Joe[15] cites 21 cases of arthritis with ankylosis of a shoulder in 1 case. Place[24] had 3 joint effusions, but all recovered full joint function. Our Case 1 showed Roentgen ray evidence of bone destruction in the right wrist joint and there was permanent impairment of joint function; Case 2 recovered completely.

From these 66 cases of meningococcal arthritis, not all of which were proven, at least 8 (12%) showed permanent joint changes. If we considered only the cases proven bacteriologically the percentage would be very much increased; for example, of Schein's proven cases, all of them showed permanent joint changes. From these meager data it seems justified to say that the prognosis of meningococcal arthritis is not as favorable as the literature would lead one to believe.

Purulent meningococcal arthritis should be treated conservatively. The effusion frequently resolves spontaneously, but large ones may call for repeated aspirations. Place[24] mentions washing the joint out with physiologic saline solution, and if sterile precautions are observed this procedure may be of service. Arthrotomy seems to have no place in the treatment of meningococcal arthritis, not that it would not serve to drain infection, but because it is more radical surgery than is necessary. Although pain is said not to be a prominent feature of these effusions, it may be present as in Case 1, and appropriate splinting with plaster shells may give great comfort to the patient. Similarly, analgesics may be called for and, if pain indicates it, opiates may be resorted to, since the condition is acute rather than chronic. The wide usage of sulfonamide medications in the treatment of meningococcal infections may be expected to lessen the incidence of metastatic manifestations—arthritis among them. As some authors[15] have suggested, if arthritis persists, a second course of sulfonamide medication may be given; this would seem to be necessary only if organisms be cultured from the joint fluid.

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Comment. When arthritis is the presenting symptom of a meningococcal infection, it is not always easy to establish the etiology without awaiting cultural demonstration of the organism. In cases of chronic meningococcemia, the septicemia may exist for months prior to the development of meningitis, and the chills, fever, rash and arthralgia may be assigned to other causes than a meningococcal infection. The fever may simulate tertian or quartan malaria,[6] and the rash and enlarged spleen may lead to the mistaken diagnosis of typhoid fever or subacute bacterial endocarditis. The form of arthritis presented may duplicate that seen in gonococcal infections, and confusion on this score is enhanced by the fact that positive gonococcal complement-fixation tests have been repeatedly reported in proven meningococcal infections.[7,16,26,31] In our Case 1 the gonococcal complement-fixation test was positive on three separate occasions. The rash may take various forms and imitate Rocky Mountain spotted fever or typhus fever. Haverhill fever was strongly suspected in Case 1 because of the fulminating arthritis and the marked rash on the lower extremities. Dr. L. E. Sutton, who originally described Haverhill fever,[25] saw our case in consultation and agreed that the clinical resemblance was so striking that only bacteriologic evidence would establish the diagnosis. The confusion with Haverhill fever has been previously noted.[16]

Conclusions. The arthritis commonly referred to in connection with meningococcal infections is in most cases an acute synovitis which occurs concomitantly with the rash. Acute synovitis usually promptly subsides with complete restoration of joint function, but exceptionally the synovitis by extension leads to a purulent arthritis and effusion into the joint space. Purulent meningococcal arthritis is a relatively uncommon disease and not many cases have been proven bacteriologically. It is suggested that the prognosis of this disease is not so uniformly favorable as is usually stated in the literature. Two proven cases of purulent meningococcal arthritis are presented.

We wish to acknowledge our thanks to Dr. William B. Porter, Professor of Medicine, Medical College of Virginia, Richmond, Va., for the privilege of reporting these cases which were seen on the Medical Service of the Medical College of Virginia Hospital.

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SARCOIDOSIS OF BOECK

METABOLIC STUDIES OF 3 CASES

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SARCOIDOSIS is regarded as a generalized systemic disease which may involve almost any organ of the human body. Skin lesions of this condition were first described in 1869 by Hutchinson,[9] who later suggested the name "Mortimer's malady," because his first patient presenting these manifestations was named Mortimer. In 1889, Besnier[2] reported a somewhat similar condition involving the face, nose and ears, which was named "lupus pernio." However, it was not until 1899 that Boeck[3] published a description of "multiple benign sarcoid" involving skin, mucous membranes and lymph nodes, from which the term sarcoidosis is taken. Following this, Heerfordt[8] described the uveoparotid syndrome, Kuznitsky and Bittorf[15] reported pulmonary lesions, and Jungling[12] published reports concerning alterations in bone. To Schaumann[21,22] goes the credit for first suggesting in 1914 the essential identity of these apparently unrelated clinical entities as seen through the eyes of dermatologists, ophthalmologists and other specialists. Schaumann pointed out that sarcoidosis may exist in the absence of cutaneous lesions and that the lymph nodes, tonsils, liver, spleen, bone marrow and lungs are frequently involved.

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Recently, pulmonary lesions with and without hilar lymphadenopathy have been reported[14] that have certain characteristics in common. These lesions have been variously named as granulie froide, chronic miliary tuberculosis,[25] pulmonary tuberculids and granulie discrete. As seen on the chest roentgenogram, they are distributed fairly symmetrically and may consist of pseudomiliary or larger foci. Clinically these pulmonary findings are identical with those frequently seen in patients with the lupus pernio of Besnier, Boeck's sarcoid, or Heerfordt's uveoparotid syndrome. This fact alone offers some justification to Schaumann's contention that the identity of the conditions is the same. Additional interest in the problem of sarcoidosis was stimulated in this country by Longcope and Pierson,[16] whose work added further support to Schaumann's observations. In 1938 Pinner[18] reported clinical, histologic and biologic similarity in many cases diagnosed as Boeck's sarcoid, uveoparotid fever, Mikulicz's syndrome, ostitis tuberculosis multiplex cystoides and a number of disseminated pulmonary and lymph node lesions.

The etiology of this condition remains unsettled. Reported cases vary in age from a few months to 60 or more years; however, more cases seem to occur in the 3rd or 4th decade of life. Earlier case reports were mostly of white patients, but a high percentage of recent cases reported were Negro patients. The two sexes seem to be about equally involved. Boeck suggested defective blood formation or autointoxication, while Schaumann assumed a tuberculous etiology (probably bovine) and cited several instances in which autopsies ultimately disclosed diffuse, caseating tuberculosis. Pinner regards sarcoidosis as a form of "non-caseating tuberculosis," and states that the sarcoid tubercle must be considered an extreme form of productive reaction in tuberculosis. As further proof, Pinner adds that "in undoubted foci tubercle bacilli are increasingly difficult to demonstrate the more the productive lesions predominate." Biologically it is interesting to note that a large percentage of these patients react only slightly or not at all to tuberculin. Pinner and co-workers[19] utilize this fact in supporting the tuberculous etiology of sarcoidosis because it has been shown that rats respond to the introduction of tubercle bacilli by the formation of lesions that greatly resemble the sarcoid lesions in man, and that rat serum contains tuberculin neutralizing factors (anticutins). English workers[14] have explained the features of sarcoid disease as a result of moribund or dead tubercle bacilli passing into the circulation and producing generalized lesions. Williams and Nickerson[26] prepared an antigen from sarcoid tissue which in 4 cases produced skin reactions within 24 hours by intradermal test. They suggested that, as in the case of lymphogranuloma inguinale, sarcoid is probably also a virus disease. Rubin and Pinner[20] have recently reviewed the autopsied cases in the literature and concluded that they could add little to the solution of the etiologic question.

Pathologically, the typical lesion is the so-called "hard tubercle," which consists of a microscopic collection of large, pale staining, polygonal, epithelioid cells forming a mass about the size of a miliary

tubercle. Although these cells are not always concentrically arranged, they may be fitted together like tiles in the floor. These clusters of cells are usually isolated, have a minimal peripheral inflammatory reaction, and are without central necrosis, according to some investigators.[3,17,18] Rubin and Pinner,[20] however, report caseation and necrosis in a few cases. Giant cells are common but not always present, and may contain inclusions of various sizes and shapes which stain with hematoxylin. Another characteristic of these lesions is that acid-fast rods are usually not demonstrable and that they are usually sterile, both in culture and in animal inoculations. The tubercles are reported to remain unchanged for long periods of time and to increase in numbers, rather than in size. They heal by a process of fibrosis and hyalinization. These sarcoid lesions may occur in any organ of the body but are prone to appear in lymphoid tissues.

The signs and symptoms of the disease vary with the location and extent of the lesions. Malaise, weakness, drowsiness, anorexia, weight loss, low grade fever, night sweats, dry mouth and generalized aches and pains are found in some patients. Dyspnea and right heart failure have been found in individuals with diffuse pulmonary involvement[1] and a chronic non-productive cough is not uncommon where the lungs or mediastinal lymph nodes are involved. Patients with Heerfordt's syndrome may complain of puffiness of the eyelids, failing vision, facial paralysis and parotid swelling. Involvement of the bones of the hands or feet may prompt complaints of swelling or pain in the fingers or toes. Tillgren[24] has reported diabetes insipidus, while Longcope[17] mentions a patient with involvement of testes and epididymis and subsequent loss of secondary sexual characteristics. Cases of generalized sarcoidosis with electrocardiographic and other evidences of cardiac involvement which may vary in different patients are also reported.[11] Patients may present themselves with skin lesions or enlarged glands and have no complaints except awareness of their physical findings.

Laboratory studies may reveal a leukopenia with a relative increase in monocytes or eosinophils, while the red blood count usually falls within normal limits. Metabolic studies have revealed elevation of serum protein with reversal of the albumin-globulin ratio. Harrell[7] has reported blood calcium values at or above the upper limit of normal in 6 of 11 cases, phosphatase levels (presumably alkaline phosphatase determinations) above normal in 7 cases, and blood cholesterol values within normal limits in all patients.

Diagnosis is based on the history of skin lesions, possible lymphadenopathy, Heerfordt's syndrome, tired feeling, irregular fever, failing vision, cough and other symptoms previously mentioned. Slit-lamp examination may reveal an active uveitis, even in the absence of eye complaints. Roentgenographic studies of the chest may reveal hilar and pulmonary involvement and Roentgen rays of the hands and feet may show areas of rarefaction and reticulation distributed throughout the medulla of the phalanges, sometimes with irregular enlargement and distortion of the bones, but without involvement of the periosteum

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or of the joints.[23] Tuberculin tests are usually negative in these patients. Blood studies as previously mentioned may aid in the diagnosis. Biopsy of one of the lymph nodes is necessary for absolute diagnosis.

Prognosis in sarcoidosis is disputed and depends on such factors as age, location and extent of lesions, presence of cardiac lesions, and presence of secondary infection. Spontaneous healing of the lesions has occurred in some patients,[13] while other cases succumb to tuberculosis, cardiac failure, or some other associated condition.

Treatment has been largely symptomatic. Boeck suggested arsenic, while more recently Roentgen ray therapy has been tried. Ophthalmologists have suggested fever therapy in cases of uveoparotid fever.

Case Reports. The following 3 cases are presented, both because of fairly complete metabolic studies having been determined, and because they include 2 additional cases of uveoparotitis.

FIG. 1.—Photograph of Case 1 showing enlarged right lacrimal gland and bilateral parotid enlargement.

CASE 1. E. M. C., a 19 year old colored female, was admitted to Charity Hospital January 29, 1944. Her illness began in September, 1943, when slightly painful swellings at the angle of both jaws were noticed. About the same time she observed that a non-productive cough had developed. In November, 1943, haziness of vision in the right eye first developed. Three days prior to admission puffiness about the eyes developed. The patient had mumps at the age of 6. There was no history of tuberculosis in the family.

Physical examination on admission revealed enlargement of both lacrimal glands (Fig. 1); both parotid glands were enlarged, especially the right, and were not tender. Examination of the right eye showed a large, inflammatory

cauliflower cyst of the iris at 7 o'clock near the margin and a smaller cyst of the iris at 5 o'clock nearer the base (Fig. 2). Slit-lamp study of the right eye revealed numerous, grayish, keratitic precipitates of various sizes, and inflammatory cells were present in the aqueous humor. Many postsynechial and lens precipitates were also seen. The left eye appeared normal. The inguinal nodes were moderately enlarged and the epitrochlear nodes were palpable bilaterally. The remainder of the physical examination was negative.

FIG. 2.—View of right eye of Case 1. Notice cysts of the iris.

Laboratory Data. R.B.C, 4,720,000; hemoglobin, 103% (14.9 gm., Hellige); W.B.C, 1800; neutrophils, 47%; eosinophils, 6.5%; basophils, 1.5%; monocytes, 14%; lymphocytes, 31%; platelets, 174,000 (direct); hematocrit (Wintrobe), 44; mean corpuscular volume, 93 microns; mean corpuscular hemoglobin, 31 micromicrograms; and sickling preparation negative. Kline and Kolmer were negative. Blood chemical studies were as follows: serum protein, 8 mg. %; albumin-globulin ratio, 1.0–1.1; blood urea nitrogen, 12.5 mg. %; cholesterol, 156 mg. %; icterus index, 6; serum calcium, 9.9 mg. %; serum phosphorus, 4.5 mg. %; serum alkaline phosphatase, 12.2 (Bodansky units); serum acid phosphatase, 0.8 (normal 0.5–2.5 units); and serum chlorides, 580 mg. %. Sternal bone marrow was normal. Agglutinations for typhoid, para-typhoid A and B, brucellosis, tularemia, and typhus fever were negative. Urinalysis was negative. Sodeman-Engelhardt urinary concentration test showed maximum specific gravity of 1.024 at the end of 2 hours. Phenolsulphonephthalein test revealed 80% excretion at the end of 1 hour. Bence-Jones protein was not found in the urine. Mantoux tests were negative. Sputum was repeatedly negative for tubercle bacilli. Stools were negative. Vital capacity was 2800 cc. (75% normal). Roentgenogram of the chest (Fig. 3) revealed bilateral hilar enlargement with diffuse infiltration throughout both lungs which appeared to radiate out from the hilum. Roentgenographic examination of the hands, feet, long bones, skull, and pelvis were normal. Electrocardiogram was within normal limits. Biopsy of inguinal nodes on 2 occasions as reported by Dr. Ernest Stark, Department of Pathology, Tulane University of Louisiana School of Medicine, revealed (Fig. 4) "almost complete replacement of the normal lymph node architecture by small and medium sized circumscribed areas composed chiefly of large epithelioid cells arranged in a concentric manner, with a moderate number of lymphocytes near the periphery. Fibers of hyaline connective tissue surround each lesion and delimit it from its neighboring lesion. Giant cells are present in an occasional lesion. Caseation necrosis is minimal and is present only in a few of the circumscribed areas."

The first week in the hospital this patient ran an irregular low grade fever which was never greater than 99.6°. Repeated chest roentgenograms and blood studies were essentially the same as on admission. The patient im-

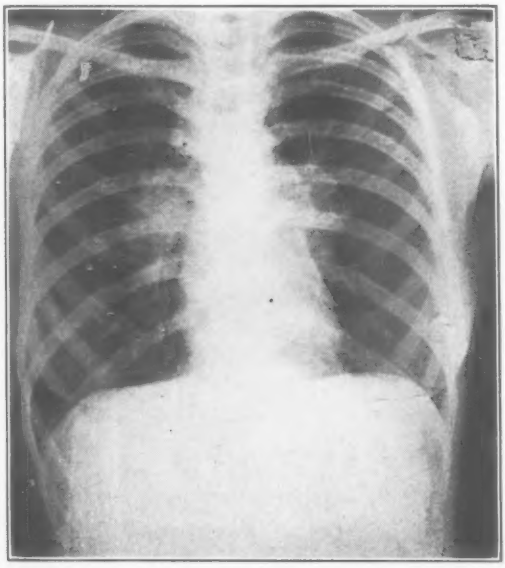

FIG. 3.—Chest roentgenogram of first patient revealing marked bilateral hilar enlargement with diffuse infiltration radiating toward the periphery.

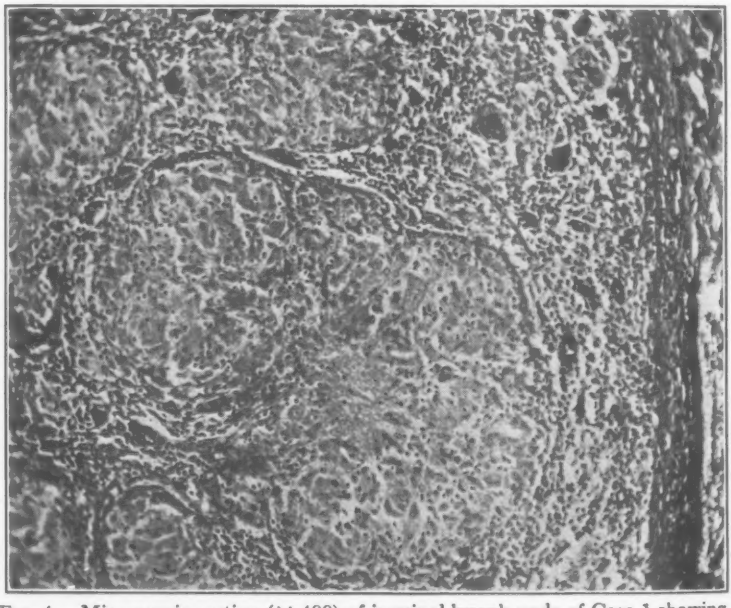

FIG. 4.—Microscopic section (× 400) of inguinal lymph node of Case 1 showing sarcoid lesion.

proved clinically and was discharged to the out-patient department on March 4, 1944.

Case 2. H. J., a 16 year old colored male, was admitted to the hospital February 3, 1944, with complaints of malaise and a chronic cough since December, 1943. His cough had been non-productive. A history of a 25 pound weight loss in the past year was obtained, and a story of pleuritic pain on the right side 6 months prior to admission was given. There was no history of contact with tuberculosis.

Physical examination revealed a generalized enlargement of the cervical lymph nodes, while there was a suggestive enlargement of the right parotid gland. The axillary nodes were also enlarged but non-tender. The lacrimal glands were not palpable and slit-lamp examination showed both eyes to be apparently normal. The remainder of the physical examination was normal.

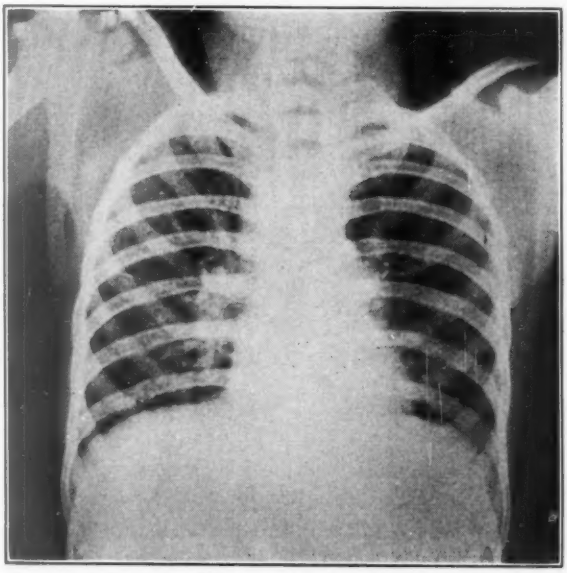

Fig. 5.—Chest roentgenogram of Case 2. Notice hilar enlargement, thickened interlobar pleura on right, and diffuse infiltration.

Laboratory Data. R.B.C., 5,540,000; hemoglobin, 90% (13 gm., Hellige); W.B.C., 5550; neutrophils, 65.5%; eosinophils, 5 %; basophils, 0.5%; monocytes, 16%; lymphocytes, 13%; platelet count, 68,400 (direct); hematocrit (Wintrobe), 40; mean corpuscular volume, 72 microns; mean corpuscular hemoglobin, 23 micromicrograms; and sickling preparation, negative. Bone marrow was normal. Kline and Kolmer tests were negative. Blood chemical studies were as follows: blood urea nitrogen, 14.3 mg. %; blood sugar, 96 mg. %; icterus index, 8.6; cholesterol, 196 mg. %; serum protein, 9.64 mg. %; albumin-globulin ratio, 1.0–1.2; serum calcium 11 mg. %; serum phosphorus, 4.5 mg. %; serum alkaline phosphatase, 17.5 (Bodansky units); and serum acid phosphatase, 2.4 (0.5–2.5 units, normal). Agglutinations for typhoid, paratyphoid A and B, brucellosis, tularemia, and typhus fever were negative. Stools were negative. Urinalysis was negative. Phenolsulphonephthalein test revealed 65% excretion at the end of 2 hours. Sodeman-Engelhardt urinary concentration test disclosed maximum specific gravity of 1.028 at the end of 2 hours. Bence-Jones protein was not found in the urine. Mantoux tests were repeatedly negative. Sputum examinations did not reveal tubercle bacilli. Vital capacity was 3100 cc. (70% of normal). Electrocardiograms were

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normal. Roentgenographic examination of the chest (Fig. 5) revealed bilateral hilar enlargement, thickening of the interlobar pleura on the right side, and diffuse infiltration radiating out from the hilar regions (more marked on the right). Roentgen ray studies of the bones of the hands, feet, skull, pelvis, and spine were negative. Biopsy of an axillary node revealed a microscopic picture almost identical with that described in the first case.

This patient had no temperature elevation during his period of hospitalization, except for a period of 36 hours following lymph node biopsy. He was comfortable during hospitalization and blood chemistries and roentgenographic findings did not change appreciably. He was discharged to the out-patient department March 17, 1944.

FIG. 6.—Photograph of Case 3. Notice right lacrimal and bilateral parotid enlargement.

CASE 3.* F. J., a 17 year old colored male, was admitted to the hospital March 3, 1944, from the out-patient department because of generalized lymph node enlargement. He became aware of swelling of the neck early in January, 1944, and coughed frequently. This patient also gave a history of fever and night sweats. He had previously had mumps and gave no history of contact with tuberculosis.

Physical examination on admission revealed a temperature of 100° F. Cervical, axillary, epitrochlear, and inguinal lymph nodes were moderately enlarged, discrete, non-tender and were not attached to skin or bone. Lacrimal and parotid glands were not enlarged. Eyes appeared to be normal. The remainder of the physical examination was negative. On March 5, 1944, it was noticed that the patient's parotid glands were enlarging (Fig. 6), were firm, and not tender. The right lacrimal gland was enlarged at this time. On

* F. J. (Case 3) developed a small pleural effusion on the right in May, 1944. Thoracentesis was done, and 2 guinea pigs were injected without producing evidences of tuberculosis or other diseases. The patient deserted the hospital in June, 1944, and was next seen on October 5, 1944, at which time he complained of fever, sweats, and expectoration of bloody sputum. Roentgenogram of the chest at this time revealed an extension of the infiltrative process with several small areas suggestive of cavitation in the right upper lobe. Two of three sputum examinations have been positive for tubercle bacilli.

March 6, 1944, slit-lamp examination of the right eye revealed numerous, scattered keratitic precipitates of various sizes, mostly grayish in color. Numerous inflammatory cells were seen in the aqueous humor while the anterior vitreous showed many scattered, grayish, inflammatory, cellular infiltrations. Findings in the left eye were similar but less marked. On March 30, 1944, skin lesions were first noticed on the lateral aspects of both thighs. These lesions were small, firm, and slightly elevated. They were somewhat paler than the surrounding skin areas.

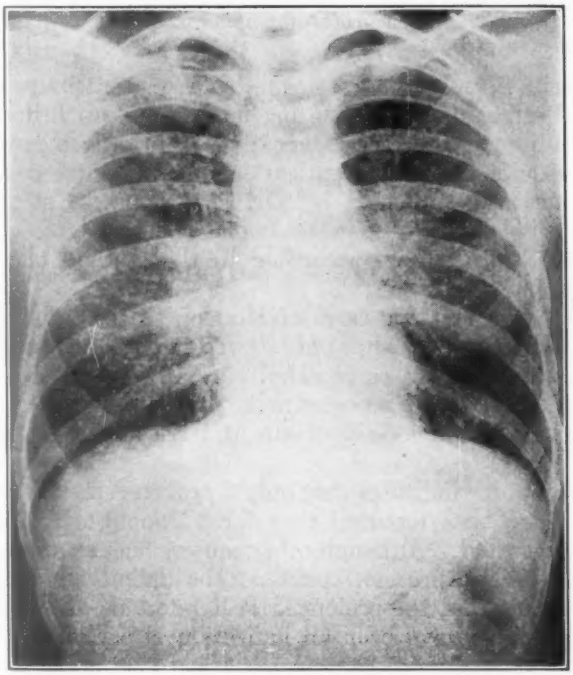

FIG. 7.—Chest roentgenogram of Case 3. Notice bilateral hilar enlargement with diffuse infiltration of both lungs which is more marked centrally and fades peripherally.

Laboratory Data. R.B.C., 4,600,000; hemoglobin, 92% (13.3 gm., Hellige); W.B.C., 6200; neutrophils, 66%; eosinophils, 6%; basophils, 1%; monocytes, 16.5%; lymphocytes, 10.5%; platelet count, 120,000 (direct); hematocrit (Wintrobe), 40; mean corpuscular volume, 80 microns; mean corpuscular hemoglobin, 28 micromicrograms; and sickling preparation was negative. Bone marrow was normal. Kline and Kolmer were negative. Blood chemical studies were as follows: blood urea nitrogen, 9.5 mg. %; blood sugar, 89 mg. %; icterus index, 8; cholesterol, 240 mg. %; serum chlorides, 590 mg. %; serum protein, 8.9 mg. %; albumin-globulin ratio, 1.0–1.1; serum calcium, 10.4 mg. %; serum phosphorus, 4.5 mg. %; serum alkaline phosphatase, 11.2 (Bodansky units); and serum acid phosphatase, 2.2 (normal, 0.5–2.5 units). Agglutinations for typhoid, paratyphoid A and B, brucellosis, tularemia, and typhus fever were negative. Urinalysis was negative. Sodeman-Engelhardt urinary concentration test disclosed a maximum concentration of 1.028. Phenolsulphonephthalein test revealed 80% excretion at the end of 2 hours. The urine did not contain Bence-Jones protein. Mantoux test was 2+ positive (1–1000). Sputum examinations were negative for tubercle bacilli and fungi. Sputum cultures were negative. Electrocardiograms revealed a P–R interval

of 0.20 second which was considered long for age and heart rate (88). Roentgenographic examination of the chest (Fig. 7) revealed bilateral hilar enlargement and infiltration in both lungs, the infiltration being more marked centrally and fading out peripherally. Roentgen rays of the bones of the hands, feet, skull, pelvis, and spine were regarded as normal. Biopsy of an axillary lymph node revealed a microscopic picture compatible with sarcoidosis. Biopsy of a skin lesion also disclosed microscopic lesions considered typical of sarcoidosis.

This patient has remained in the hospital for a period of 6 weeks and his temperature has varied from 99.0° to 102.4° F. daily. He has lost 10 pounds during hospitalization. Repeated roentgenographic and blood studies have added little of value. His electrocardiograms continue to show an abnormally long P–R interval of 0.20 second.

Discussion. Some effort was made by us to contribute toward the etiology of sarcoidosis. Guinea pig inoculations with material from the first and second cases were negative. An antigen prepared from a lymph node of the second patient failed to produce positive intradermal reactions. An effort by Dr. Ernest Stark, Department of Pathology, Tulane University of Louisiana School of Medicine, to demonstrate "anticutins," according to the method of Pinner and co-workers,[19] was unsuccessful.

In 1940 only about 100 cases of Heerfordt's syndrome were to be found in the literature,[4,6] while only 20 were from North America. The author has found 10 cases reported since 1940. Uveoparotitis was present in 2 of the 3 cases reported here. Each of these cases presented pulmonary and lymph node involvement, while skin lesions were found in only 1.

A recent report[11] indicates that only 8 proven cases of sarcoidosis of the heart have been reported thus far. Undoubtedly, many other cases have occurred. Although other causes, such as an unrecognized previous rheumatic process, could not be definitely excluded, it is entirely possible that the prolonged P–R interval (0.2 second) of the third patient may have been an indication of sarcoid lesions in the heart.

Leukopenia and eosinophilia were demonstrable in each of the cases reported. Red blood counts and hemoglobin values were essentially normal.

Although Harrell[7] reported in 1940 that serum phosphatase levels are increased in sarcoidosis, no technique was generally available at that time[5,10] to determine serum acid phosphatase values. Serum alkaline phosphatase levels were elevated in each of these 3 cases, while serum acid phosphatase values were not affected.

Blood calcium, phosphorus, cholesterol, glucose and urea studies revealed values within the generally accepted limits of normal.

Summary. 1. A brief review of the historical, etiologic, pathologic and clinical aspects of sarcoidosis is given.

2. Three cases, including 2 with Heerfordt's uveoparotid syndrome, are presented.

3. The possibility of sarcoid lesions of the heart in 1 case is discussed.

4. Serum acid phosphatase values of these 3 cases were found to be within normal limits, while serum alkaline phosphatase values were elevated.

5. Other metabolic studies merely confirm findings previously reported by other investigators.

6. No additional information concerning the etiology was revealed by these studies.

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ELECTROPHORETIC ANALYSIS OF PLASMA PROTEINS IN HYPERTHYROIDISM AND HYPOTHYROIDISM

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Studies of the plasma proteins in thyroid disease have been rather fragmentary. In 1932 Shirer[14] reviewed the literature and reported 75 cases in which the total serum protein, albumin, euglobulin, pseudoglobulin I, and pseudoglobulin II were determined. In hyperthyroidism he found a definite decrease in serum albumin and an increase in total globulin. There was a decrease in pseudoglobulin II, while pseudoglobulin I and euglobulin were increased. The average albumin-globulin ratio ranged from 0.61 to 0.70 in different groups. In hypothyroidism reversal persisted, the ratio being 0.89 in 12 cases.

Our studies were undertaken because fractionation of serum proteins

by the salting-out technique is open to considerable criticism and because electrophoretic analyses of plasma proteins in thyroid disease have not been reported.

Methods. *Protein Studies.* A fasting blood sample was taken and oxalated, using 1.5 mg. potassium oxalate per milliliter of blood. The blood was immediately centrifuged at high speed and the plasma removed. Total plasma nitrogen was determined on an aliquot of plasma by the Pregl[13] modification of the micro-Kjeldahl method. If the blood urea nitrogen was within normal limits, a non-protein nitrogen correction of 25 mg. per 100 ml. was used. If the blood urea nitrogen was elevated, the non-protein nitrogen was determined and the proper correction made. The value 6.25 was the protein factor used. Five ml. of plasma was diluted 1 to 4 with phosphate buffer of pH 7.8 and ionic strength 1.6. The diluted plasma was dialyzed 72 hours at approximately 3° C. in a cellophane sac against the phosphate buffer solution. At the end of dialysis the diluted plasma was centrifuged at high speed. Studies were done in the Tiselius electrophoresis apparatus by Longsworth's[8] modification of the Tiselius method. Pattern areas were determined by the procedure of Tiselius and Kabat.[15]

TABLE 1.—PLASMA PROTEIN FRACTIONS OF NORMAL SUBJECTS

Subj.		Total protein	Albumin		α-Globulin		β-Globulin		γ-Globulin		Fibrinogen		
No.	Sex	(gm.*)	Gm.*	%†	Gm.*	%†	Gm.*	%†	Gm.*	%†	Gm.*	%†	A/G‡
1	F	6.85	4.48	65.6	0.50	7.3	0.80	11.7	0.79	11.6	0.26	3.8	2.12
2	F	6.93	4.42	63.9	0.49	7.1	0.97	14.0	0.85	12.2	0.20	2.8	1.90
3	F	7.46	4.53	60.9	0.65	8.7	1.02	13.5	0.91	10.1	0.35	6.8	1.75
4	F	6.33	4.02	63.4	0.52	8.1	0.78	12.3	0.78	12.2	0.22	3.2	1.93
5	F	6.52	3.97	60.8	0.52	8.0	0.88	13.4	0.72	11.1	0.43	6.7	1.87
6	M	6.31	3.84	60.9	0.41	6.5	1.00	15.9	0.76	12.0	0.30	4.7	1.77
7	F	7.82	5.11	65.3	0.66	7.2	1.07	13.7	0.76	9.7	0.32	4.1	2.14
8	F	6.57	3.97	60.3	0.55	8.4	0.73	11.3	0.90	13.7	0.42	6.4	1.84
9	M	6.09	3.74	61.4	0.51	8.4	0.68	11.2	0.90	14.8	0.26	4.2	1.79
10	M	5.94	3.84	64.6	0.40	6.6	0.65	11.0	0.71	12.0	0.34	5.8	2.18
11	M	6.39	4.19	65.6	0.42	6.5	0.86	13.5	0.55	8.6	0.37	5.8	2.28
12	F	6.66	4.12	61.9	0.47	7.1	0.84	12.5	0.75	11.3	0.48	7.2	2.00
13	F	6.87	4.21	61.3	0.42	6.1	0.99	14.4	0.83	12.1	0.42	6.1	1.88
14	M	6.58	4.08	60.5	0.40	6.0	0.90	12.9	0.90	12.9	0.50	7.7	2.04
15	F	5.98	4.02	67.2	0.40	6.6	0.67	11.3	0.60	10.0	0.16	4.9	2.22
16	M	6.40	4.25	66.3	0.50	7.8	0.78	12.3	0.63	9.8	0.24	3.8	2.22
17	M	6.48	3.90	60.1	0.43	6.6	0.92	14.3	0.87	13.5	0.36	5.5	1.75
18	M	6.12	3.76	61.5	0.42	6.9	0.84	13.7	0.77	12.5	0.33	5.4	1.85
19	F	5.99	3.72	62.1	0.39	6.5	0.77	12.7	0.74	12.2	0.39	6.5	1.98
20	F	6.25	3.95	63.3	0.41	6.5	0.96	15.4	0.71	11.3	0.22	3.5	1.90
21	M	6.12	3.82	62.3	0.46	7.5	0.81	13.3	0.70	11.5	0.33	5.4	1.94
Average	..	6.51	4.09	62.7	0.47	7.2	0.81	13.1	0.77	11.7	0.33	5.4	1.97
Range	..	5.94–7.82	3.72–5.11	60.1–67.2	0.39–0.66	6.0–8.7	0.65–1.07	11.0–15.9	0.60–0.91	8.6–14.8	0.16–0.48	2.8–7.2	1.75–2.28

* Grams per 100 ml. plasma.
† Percentage of total protein.
‡ Albumin-globulin ratio calculated on serum basis.

Subjects. Control values were determined on blood from 21 laboratory workers and physicians. These subjects were from 20 to 45 years old and had no abnormal physical findings.

Twenty patients with hyperthyroid or hypothyroid symptoms were studied. In all hyperthyroid cases an elevated basal metabolic rate with concurrent physical findings typical of the disease was present. Criteria for decreased thyroid function were an abnormally low basal metabolic rate, myxedema, and elevated blood cholesterol in addition to characteristic physical abnormalities.

Twelve patients were studied who had progressive exophthalmos following thyroidectomy or Roentgen ray irradiation of the thyroid. Their basal metabolic rates were within normal limits, and exophthalmos was the only remaining visible symptom of the thyroid syndrome.

Results. Normal values agree closely with those reported by Longsworth and co-workers,[9] Luetscher,[10] and Moore and Lynn as cited by Abramson and co-workers[1] (see Table 1).

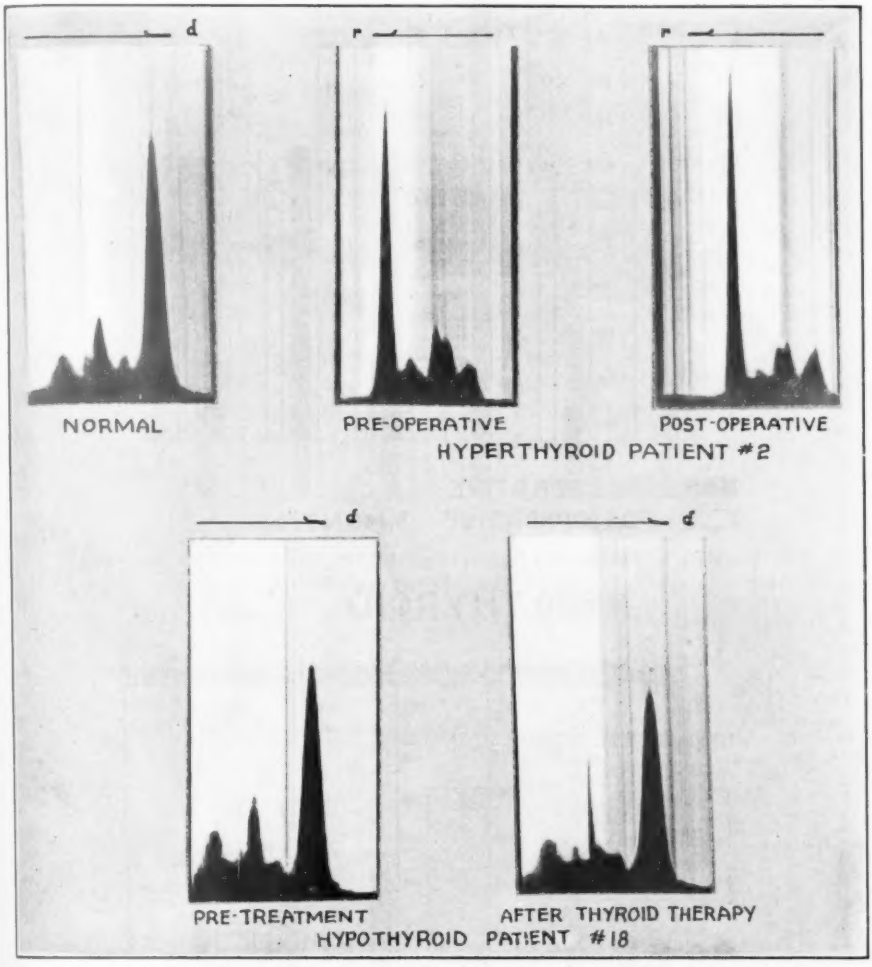

FIG. 1.—Electrophoretic patterns of the descending boundaries of normal human plasma, of the ascending boundaries of plasma from a hyperthyroid patient before operation and 4 months after operation, and of the descending boundaries of plasma from a hypothyroid patient before and after thyroid therapy.

Table 2 gives results for patients with hyperthyroid or hypothyroid symptoms. Series for the same patient are listed as *a*, *b*, and *c* under the patient's number. Successive tests on hyperthyroid Patient 2 and hypothyroid Patient 18 are shown in Figure 1. Figure 2 presents data on Patient 1, a typical hyperthyroid, before and after treatment. Figure 3 represents a series of studies on hypothyroid Patient 17, and Figure 4 a series on Patient 20, a cretin. Values for Patient 25, who had progressive exophthalmos, are seen in Figure 5.

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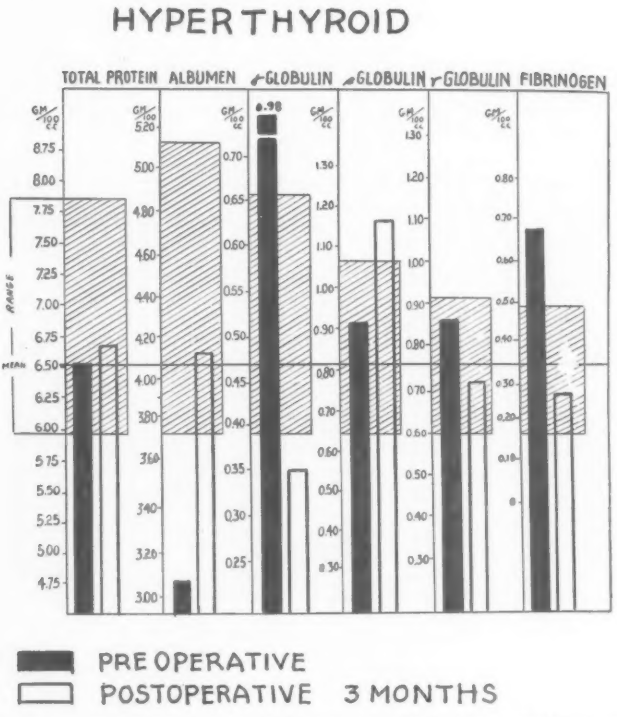

FIG. 2.—Data on Patient 1, a typical hyperthyroid, before and after treatment.

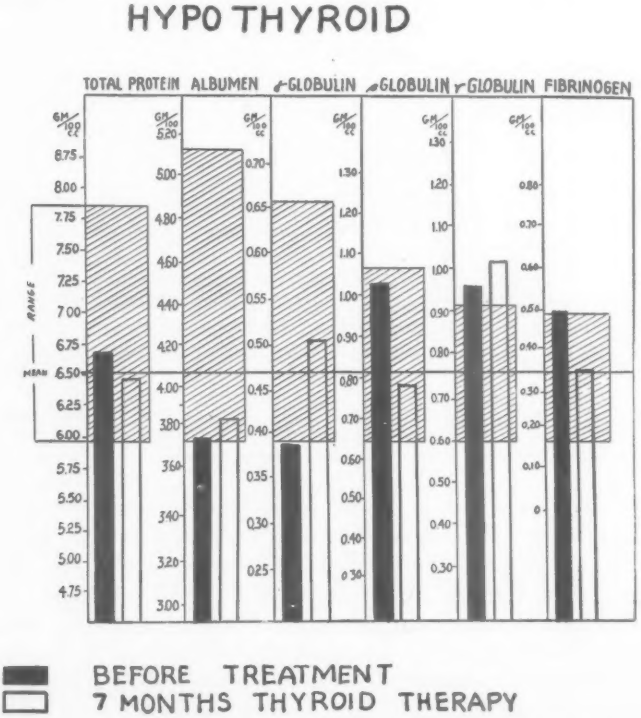

FIG. 3.—Results of a series of studies on hypothyroid Patient 17.

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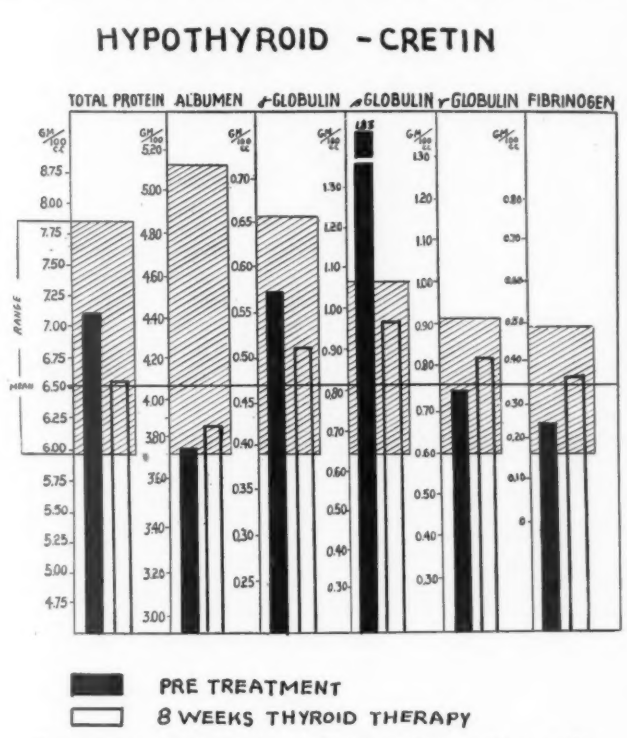

FIG. 4.—Results of a series of studies on Patient 20, a cretin.

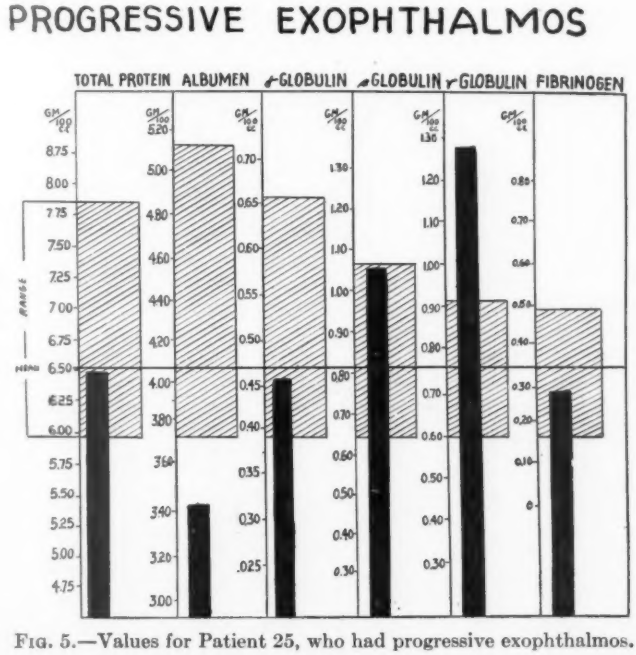

FIG. 5.—Values for Patient 25, who had progressive exophthalmos.

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TABLE 2.—PLASMA PROTEIN FRACTIONS OF PATIENTS WITH THYROID DISEASE

Case No.	Type of case	Total protein (gm.*)	Albumin		α-Globulin		β-Globulin		γ-Globulin		Fibrinogen		A/G‡	Body weight change (lb.)
			Gm.*	%†	Gm.*	%†	Gm.*	%†	Gm.*	%†	Gm.*	%†		
1	Hyperthyroid													
	a. Preoperative	6.51	3.07	47.3	0.98	14.9	0.91	13.9	0.87	13.4	0.68	10.5	1.11	−30 in 8 mos.
	b. 3 mos. postoperative	6.65	4.13	62.0	0.35	5.2	1.17	17.7	0.72	10.9	0.28	4.2	1.84	+20
2	Hyperthyroid													
	a. Preoperative	6.37	3.58	56.2	1.03	16.1	0.63	9.9	0.78	12.1	0.35	5.5	1.46	−16 in 3 yrs.
	b. 4 mos. postoperative	6.02	3.58	59.4	0.47	7.8	0.65	10.8	0.77	12.8	0.55	9.2	1.90	
3	Hyperthyroid													
	Preoperative	6.75	3.42	51.0	1.00	14.8	1.05	15.4	0.69	10.1	0.59	8.7	1.25	+16 (increased appetite)
4	Hyperthyroid													
	Preoperative	6.31	3.48	55.0	0.71	11.2	0.78	12.5	0.75	11.9	0.59	9.4	1.55	−15
5	Hyperthyroid													
	2 days postoperative	5.05	2.45	48.5	0.53	10.4	0.92	18.3	0.72	14.2	0.43	8.6	1.13	
6	Hyperthyroid													
	2 days postoperative	6.00	3.45	57.4	0.48	8.1	0.72	12.1	0.64	10.7	0.70	11.7	1.86	−10
7	Hyperthyroid													
	Preoperative	6.40	3.62	55.1	0.92	14.3	0.89	13.9	0.66	10.3	0.41	6.4	1.52	
8	Hyperthyroid													
	Preoperative	6.96	3.56	51.1	0.84	12.1	1.27	18.3	0.92	13.2	0.37	5.3	1.10	−10
9	Hyperthyroid													
	Preoperative	6.56	3.70	56.4	0.70	10.6	1.06	16.1	0.60	9.2	0.50	7.7	1.56	−8
10	Hyperthyroid													
	Preoperative	5.50	3.03	55.1	0.47	8.5	0.85	15.4	0.77	14.0	0.38	7.0	1.45	
11	Hyperthyroid													
	Preoperative	6.68	3.77	56.4	0.67	10.0	1.39	20.9	0.51	7.6	0.34	5.1	1.47	−10
12	Hyperthyroid													
	Preoperative	6.64	3.64	54.8	0.76	11.4	1.00	15.0	0.81	12.3	0.43	6.5	1.41	0
13	Hyperthyroid													
	a. Preoperative	6.56	3.55	54.1	0.73	11.2	0.87	13.3	0.93	14.1	0.48	9.4	1.38	−15
	b. 9 mos. postoperative	7.02	4.02	58.8	0.63	8.9	0.99	14.1	0.99	14.1	0.29	4.1	1.48	+7
14	Hyperthyroid§													
	Preoperative	4.85	2.76	57.0	0.51	10.4	0.64	13.2	0.61	12.5	0.33	6.9	1.57	
15	Hypothyroid													
	a. Pretreatment	6.59	3.46	52.6	0.34	5.1	1.07	16.2	1.33	20.2	0.39	5.9	1.26	
	b. Fed thyroid 2 wks.	6.67	3.50	52.5	0.34	5.1	1.28	19.2	1.15	17.0	0.40	6.1	1.26	
	c. Fed thyroid 5 wks.	6.77	3.76	55.5	0.56	8.3	0.94	13.9	1.01	14.9	0.50	7.4	1.50	
	a. Pretreatment	6.08	3.09	50.2	0.33	4.9	1.14	17.2	1.10	16.5	0.42	6.2	1.43	
	b. Fed thyroid 3 wks.	6.42	3.35	52.2	0.44	6.8	1.00	15.5	1.09	17.0	0.54	8.5	1.33	
	c. Fed thyroid 5 wks.	6.29	3.58	56.8	0.43	6.9	0.91	14.4	0.98	15.5	0.39	6.4	1.54	
17	Hypothyroid													

	Preoperative	4.85	2.76	57.0									
15	Hypothyroid												
	a. Pretreatment	6.59	3.46	52.6	0.34	5.1	1.07	16.2	1.33	20.2	0.39	5.9	1.26
	b. Fed thyroid 2 wks.	6.67	3.50	52.5	0.34	5.1	1.28	19.2	1.15	17.0	0.40	6.1	1.26
	c. Fed thyroid 5 wks.	6.77	3.76	55.5	0.56	8.3	0.94	13.9	1.01	14.9	0.50	7.4	1.50
	a. Pretreatment	6.08	3.09	50.8	0.33	5.4	1.14	17.2	1.10	16.5	0.42	6.2	1.43
	b. Fed thyroid 3 wks.	6.42	3.35	52.2	0.44	6.8	1.00	15.5	1.09	17.0	0.54	8.5	1.33
	c. Fed thyroid 5 wks.	6.29	3.58	56.8	0.43	6.9	0.91	14.4	0.98	15.5	0.39	6.4	1.54
17	Hypothyroid												
	a. Pretreatment	6.64	3.75	57.2	0.37	5.6	1.02	15.3	0.96	14.5	0.49	7.4	1.56
	b. Fed thyroid 6 wks.	6.27	3.80	60.5	0.50	8.1	0.56	8.8	1.02	16.3	0.39	6.3	1.83
	c. Fed thyroid 7 mos.	6.48	3.84	59.2	0.51	7.9	0.78	12.1	1.01	15.6	0.34	5.2	1.67
18	Hypothyroid												
	a. Pretreatment	6.87	3.94	57.4	0.30	4.3	1.65	24.0	0.67	9.8	0.31	4.5	1.50
	b. Fed thyroid 8 wks.	6.82	3.81	55.9	0.53	7.7	1.04	15.3	0.98	14.3	0.46	6.8	1.50
19	Hypothyroid												
	a. Pretreatment	6.95	3.90	56.1	0.44	6.4	1.20	17.2	1.10	15.8	0.31	4.5	1.42
	b. Fed thyroid 7 wks.	6.46	3.71	57.4	0.50	7.8	0.84	13.0	1.11	17.2	0.30	4.6	1.52
20	Hypothyroid cretin												
	a. Pretreatment	7.12	3.74	52.5	0.57	8.0	1.83	25.8	0.73	10.2	0.25	3.5	1.19
	b. Fed thyroid 8 wks.	6.52	3.87	59.3	0.51	7.9	0.99	15.1	0.82	12.6	0.33	5.1	1.67

* Grams per 100 ml. plasma.
† Percentage of total protein.
‡ Albumin-globulin ratio calculated on serum basis.
§ Proved liver damage.

TABLE 3.—PLASMA PROTEINS OF PATIENTS WITH PROGRESSIVE EXOPHTHALMOS BUT NO OTHER EVIDENCE OF EXOPHTHALMIC GOITER

Case No.	Previous treatment	Total protein (gm.*)	Albumin		α-Globulin		β-Globulin		γ-Globulin		Fibrinogen		A/G‡	Body weight change (lb.)
			Gm.*	%†	Gm.*	%†	Gm.*	%†	Gm.*	%†	Gm.*	%†		
21	Roentgen ray to pituitary and thyroid	5.90	3.04	51.6	0.43	7.2	1.04	17.6	1.12	19.0	0.27	4.6	1.17	0
22	Roentgen ray to thyroid	6.82	3.65	53.2	0.36	5.3	0.88	12.8	1.27	18.5	0.70	10.2	1.48	0
23	Roentgen ray to thyroid	6.21	4.02	64.6	0.55	8.8	0.76	12.5	0.51	8.2	0.37	5.9	2.20	0
24	Roentgen ray to thyroid	6.10	3.60	59.3	0.52	8.5	0.85	14.0	0.77	12.6	0.36	5.6	1.68	0
25	Thyroidectomy	6.49	3.42	52.6	0.46	7.0	1.05	16.3	1.27	19.5	0.29	4.5	1.23	0
26	Thyroidectomy	6.12	3.52	57.5	0.41	6.7	1.03	16.8	0.76	12.5	0.40	6.5	1.60	0
27	Thyroidectomy	6.34	3.44	54.3	0.39	6.0	1.13	17.9	0.89	14.0	0.49	7.8	1.43	0
28	Thyroidectomy	6.56	3.43	52.3	0.65	9.9	1.37	20.9	0.73	11.1	0.38	5.8	1.25	0
29	Thyroidectomy	6.22	3.24	52.2	0.76	12.2	0.75	12.0	0.97	15.6	0.50	8.0	1.31	0
30	Thyroidectomy	6.37	3.37	52.8	0.59	9.3	1.03	16.2	0.92	14.4	0.46	7.3	1.33	+15 in 4 mos.§
31	Thyroidectomy	6.11	3.41	55.7	0.70	11.7	0.85	14.0	0.64	10.4	0.50	8.2	1.55	0
32	Thyroidectomy	6.15	3.97	64.6	0.41	6.7	0.88	14.3	0.70	11.3	0.19	3.1	1.98	

* Grams per 100 ml. plasma.
† Percentage of total protein.
‡ Albumin-globulin ratio calculated on serum basis.
§ Basal metabolic rate −10.

In the hyperthyroid cases, the most notable and consistent deviation from the normal was a low albumin, both in grams per 100 ml. and in percentage of total protein. An increase in α-globulin was noted in many instances. In some cases the fibrinogen level was also high. In the 2 cases of greatest elevation of fibrinogen the blood was taken 2 days after operation, which may partially explain this change. The other cases were studied preoperatively.

In the cases studied several months after operation, when all symptoms of hyperthyroidism had subsided, the plasma protein picture was normal or much improved.

In contrast with patients who had no postoperative symptoms and showed a normal or nearly normal plasma protein picture was the group with progressive exophthalmos after thyroidectomy or Roentgen ray irradiation of the thyroid. Of the 12 patients studied, 10 had a strikingly abnormal plasma protein picture (Table 3).

All adult hypothyroid patients had a decrease in percentage of plasma albumin. The β-globulin was greatly elevated and the α-globulin decreased or at a low normal level, both in percentage of total protein and in grams per 100 ml. After treatment the β-globulin always fell and the α-globulin rose. In some cases the percentage of albumin increased, although the actual value in grams per 100 ml. showed no consistent change.

In the cretin case the β-globulin was much elevated, as in the adult hypothyroid cases, but the α-globulin was above normal. However, it may not be valid to compare values obtained on a child with those of normal adult controls.

The decreased plasma albumin noted in the hyperthyroid cases agreed with reported values obtained by chemical fractionation. The values observed in our cases, however, were not as low as those reported when chemical precipitation was used. The average albumin percentage in the hyperthyroid cases was 54, whereas the average normal value was 62.7. The albumin-globulin ratio was also less radically altered. The normal albumin-globulin ratio was 1.75 to 2.28; for hyperthyroids the ratio was 1.10 to 1.86.

Comment. The fact that many hyperthyroid patients have impaired liver function and histologically demonstrable liver damage suggests that liver changes may explain the decreased albumin (Beaver and Pemberton,[3] Maddock and others,[12] McIver[11]). Low serum albumin was a very characteristic change observed by Gray and Barron[6] in the electrophoretic analysis of serum proteins in diseases of the liver.

Experiments on hyperthyroid dogs by Drill and co-workers[4] disclosed greatly decreased liver function (as indicated by bromsulfalein excretion), which was evident in animals given the standard diet on an average of 45 days after beginning thyroid feeding. Administration of 10 gm. of yeast concentrate daily (equivalent to 200 U.S.P. units of vitamin B_1, 230 μg. of riboflavin, 200 μg. of vitamin B_6, and 1500 to 2000 μg. of copantothenate per gram) delayed the derangement of liver function until 90 days after initiation of thyroid feeding. These experiments suggested the interesting possibility that the patients with the greatest alteration in plasma proteins were receiving the least adequate

vitamin B-complex diet. Such a thing is difficult to prove when patients have fully developed hyperthyroidism of some duration at the time the first studies are made.

Reversible liver changes could also account for the return of plasma protein levels to normal after abatement of hyperthyroid symptoms.

The low plasma albumin observed in the hypothyroid cases agreed with reported results for thyroidectomized dogs (Goldberg[5]) and rats (Levin and Leathem[7]). In the animal experiments globulins were not fractionated. Our studies showed an increase in β-globulin and γ-globulin fractions. The plasma cholesterol was very high when the β-globulin was most elevated. Experiments of Longsworth and associates[9] on plasma from a patient with obstructive jaundice yielded a very high β-globulin value. The plasma contained a large amount of cholesterol. Extraction with ether reduced the β-globulin peak. According to Abramson and co-workers,[2] "this suggests a combination between lipids and β-globulin."

Summary. The plasma proteins of 20 hyperthyroid or hypothyroid patients were studied by the Tiselius electrophoresis method. Control values were established on 21 normal subjects.

In the 14 hyperthyroid cases the plasma albumin was below normal levels both in grams per 100 ml. and in percentage of total plasma protein. In the majority of cases the α-globulin was markedly increased. No consistent change was observed in the other globulin fractions. After thyroidectomy, when all symptoms of hyperthyroidism had subsided, the plasma protein picture was normal or had values only slightly beyond the normal range.

In the 6 hypothyroid cases there was a low plasma albumin, a low α-globulin, and an increased β-globulin. After some months of thyroid therapy the plasma protein picture approximated the normal.

In patients with progressive exophthalmos and no other residual symptoms of Graves' disease, there was a low plasma albumin but no consistent change in the globulin fractions.

Dr. Edmund E. Beard kindly furnished blood samples and clinical data on Patient 15. We wish to acknowledge the services of Mr. V. B. Seitz of the Cleveland Clinic, who helped in planning and construction of the Tiselius apparatus.

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ASPIRATION BIOPSY OF THE THYROID IN THE EVALUATION OF THYROID DYSFUNCTION*

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There are numerous clinical and laboratory tests for the diagnosis and evaluation of thyroid dysfunction. Nevertheless there is a group of cases where the laboratory and clinical findings are at variance and a diagnosis cannot be made definitely. The standard procedure for laboratory diagnosis, the basal metabolism test, has certain limitations in its interpretation.[4] Blood cholesterol levels and the galactose tolerance test are two other valuable laboratory procedures, but they, like the basal metabolism are affected by extrathyroid pathology. Other laboratory tests like the urinary creatinin, the creatinin hydrate tolerance test,[10] the complement-fixation serum test[6] and the electrical impedance angle test for thyrotoxicosis[3] have been discarded for the most part as impractical or unreliable. The blood iodine level is a valuable indicator, but like other laboratory tests is but an indirect measure of thyroid activity. Clinical tests such as the quinine tolerance test,[2] the thyroid tolerance test,[8] the adrenalin hypersensitiveness test[5] and the iodine tolerance test[9] are likewise limited in their scope and interpretation because the symptoms and signs of thyroid diseases can be closely mimicked by several other organic and functional disorders.

The direct method of tissue examination always stands as the final diagnostic criterion. Biopsy has been used to establish the diagnosis in a variety of diseases in many organs. Where the tissue is approached easily, enough can be excised for ordinary histologic section. Where it is more inaccessible, aspirations have been resorted to, using a needle and syringe. The chief difficulty encountered with aspiration biopsies is that only a very small amount of tissue is obtainable, making the ordinary histologic diagnosis often unsatisfactory.

Abel[1] has utilized a method of histologic diagnosis of thyroid disease based on a micrometric examination of the thyroid acinar cells. Because the method utilizes the dimensions of the cells themselves, and not the general architecture of the gland, it can be used with very small amounts of tissue and thus suggests that aspiration biopsies can be used for the *direct* diagnosis of thyroid disease.

Procedure. In order to make the procedure as simple and as atraumatic as possible, a technique has been followed using either a No. 18 or a No. 16 gauge 2 inch intravenous needle and an ordinary 20 cc. syringe. The needle should be sharp and the syringe fairly new so that the barrel and piston do

* Thesis submitted by the Senior author to the Faculty of the Graduate School of Medicine of the University of Pennsylvania, in partial fulfilment of the requirements for the degree of Master of Medical Science (M.Sc.[Med.]) for graduate work in Surgery.

not fit loosely. A record type or a special aspiration syringe (B. D. & Co.) may be used, but are not necessary. Tissues obtained are placed in 5% formalin and are treated as regular paraffin sections to insure uniformity of results. The tissues cannot be smeared like tumor aspirations as described by Martin and Ellis.[7] However, to obtain a quick diagnosis, rapid sections can be done as outlined by them.

The patient may be given a sedative 20 minutes before the aspiration. He should be lying flat with the neck slightly hyperextended. The gland is palpated and a small area in the midline of the neck close to the gland is prepared aseptically and a wheal is raised in the skin with 1% procaine. Some of the solution is injected continuously along the line of the intended puncture down to the gland. A small nick is made through the skin with a bistoury pointed scalpel (No. 11 B. P. blade) with the instrument held at right angles to the skin surface. This puncture of the skin facilitates insertion of the needle and prevents the needle becoming plugged with surface epithelium. The needle with the syringe attached is introduced tilted about 30 degrees to the sagittal plane. It is advanced slowly through the superficial tissues until the point is felt to enter one or the other of the lateral lobes, whichever seems more accessible. This technique will avoid the trachea, and other important

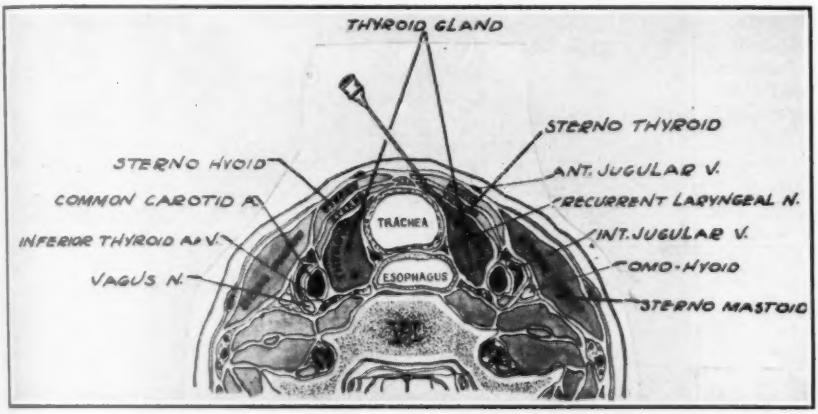

FIG. 1.—Transverse section of neck at level of sixth cervical vertebra illustrating an aspiration needle in place.

structures, as shown in Figure 1. Guided by palpation with the disengaged hand, it is striking how readily a difference in consistency of the tissues can be felt, as the point of the needle enters the gland. When the point of the needle is felt to enter the gland, the piston of the syringe is partly withdrawn so as to produce a vacuum, and the needle is then advanced 1 to 3 cm. farther, depending on the size of the gland. Maintaining the vacuum, the needle is then withdrawn to the same distance, advanced again, and withdrawn, thus maintaining the vacuum constantly and keeping the point of the needle within the gland. As the needle is advanced into the gland, a slightly rotatory motion may be given to the needle. Tissue from the gland enters the needle and is held within it both by a punch action of the advancing needle and by suction of the vacuum. Care must be taken that the vacuum is maintained while the needle is manipulated within the gland. Aspiration by suction alone, with the needle at rest, is usually not sufficient to draw tissue into the needle, and is the most common cause of failure to obtain tissue. In 23 cases we failed to obtain sufficient material for examination in 3.

Before the needle is completely withdrawn from the tissues, the piston must be slowly released, the syringe detached, and the needle withdrawn separately, otherwise any remaining vacuum may cause the aspirated material to be

suddenly drawn into and splashed over the interior of the syringe making its collection more difficult. Blood and tissue usually appear in the syringe while the needle is being advanced and withdrawn. This occurs especially in the diffuse toxic type, or so-called "blotting-paper" gland. In addition, there will most always be tissue in the needle.

After complete withdrawal of the apparatus, the syringe is partially filled with air, again attached, and the contents of the needle expelled into the specimen bottle. If tissue is obtained, the needle and syringe should then be washed with a small amount of the formalin to insure getting all of the material, as some of it may stick to the side of the needle and syringe. If no visible tissue is obtained, the procedure may be repeated, using the same or the contralateral lobe, and going through the same skin puncture.

FIG. 2.—Aspiration biopsy of the thyroid gland. (Oil immersion.)

Contrary to what might be expected, if a few minutes are spent explaining to the patient that it is a simple routine examination, it is accepted even by the toxic patient as casually as the basal metabolism test. Most patients on sight of the needle and syringe take it as "just another blood test." It can be done in a few minutes with little discomfort. Occasionally when the needle penetrates quite deeply there may be a slight pain felt in the back of the neck which disappears when the needle is withdrawn.

Thus far the procedure has been absolutely safe in our hands. The first 7 tests were done on the operating table shortly before thyroidectomy to establish the safety of the procedure. In only 1 case (the second) was there any evidence of where the point of the needle had penetrated the gland. In this case we did not conform to our now established technique, and the needle was inserted lateral to the gland and resulted in a small hematoma. We have had no untoward results from the procedure, nor any unpleasantness of any kind. Up to the present the test has been done only upon hospital cases, but there does not seem to be any reason why it cannot be done in any clinic outpatient department or doctor's office.

On microscopic examination the aspiration specimens are found to contain only small particles of the gland itself in amongst much blood. On closer

examination under the oil-immersion lens, these particles are seen to consist entirely of acinar cells, arranged in acini and portions of acini from which the colloid material is entirely gone (Fig. 2). The force of the aspiration is apparently chiefly exercised on the cells, and the colloid is squeezed out and left behind. In those cases where only single cells are left, the acinar cells appear to be intact and undistorted in their acini and remnants of acini. The cell boundaries are as easily distinguishable as in ordinary sections of thyroid. In fact, in some instances the cell borders are more difficult to delineate in whole gland sections, because of the gradual merging of globules of secretory material in the cell with colloid in the acini.

The measurement of the thyroid acinar cells as described by Abel[1] in regular thyroid sections of postmortem specimens was performed with a micrometer scale fitted into the eyepiece of the microscope and using an oil-immersion objective. The diameter of a cell was measured in all cases at a point crossing the nucleus, and on a line along the radius of an acinus. The cells were measured in blocks of 100 from 100 separate acini chosen at random according to where the scale happened to fall as the slide was systematically moved across the stage. The only provisos were that the acini be open and the cell boundaries be distinguishable.

This same technique was used in these experiments in measuring cells in control slides from operative specimens of thyroids from which aspirations had been previously obtained. In the measurement of cells from aspiration specimens, the technique had to be modified slightly because of the fact that in many instances only portions of acini were obtained in the specimens. The diameter of the cell was measured as before, across the neuclus along the apparent line of the diameter of the acinus. The cells were measured in blocks of 100 per aspiration chosen from 100 separate acini or portions of acini, chosen at random as the slide was systematically moved across the stage. The conditions for measurement were that the cell boundaries be distinct, and sufficient of the acinus be left that its apparent contour and radius be readily seen.

With this procedure 100 cells from each of 20 aspiration specimens were measured. Later, sections from surgical specimens were obtained from each of 17 glands (aspiration was done on 3 normal patients with other surgical disorders) and 100 cells from each were measured and the results were compared with those from the aspirations.

Findings. Abel[1] used the criterion that an average cell height of over 5.8 units indicated toxicity in nodular goiters; a height of over 5 units indicated toxicity in diffuse goiters, and a height of less than 5 units indicated a normal gland. Each of his units equalled 1.4 microns giving us the following standards to go by:

1. An average cell height of over 8.1 microns indicates toxicity in nodular goiters.
2. An average cell height of over 7 microns indicates toxicity in diffuse goiters.
3. An average cell height under 7 microns indicates a normal gland.

Using these standards we found that the measurements from all the aspirations were of the magnitude expected (Table 1).

The measurements obtained from the aspiration specimens compared very closely to the measurements obtained from the surgical specimens. The greatest discrepancy was only of a magnitude of 0.7 micron in Cases 1, 6 and 10.

We were able to make the diagnosis of toxicity in 16 cases of the 17 cases examined. In 5 cases of nodular thyroids we were able to establish toxicity and in 11 cases of diffuse hyperthyroidism the diag-

TABLE 1.—CASES OF HYPERTHYROIDISM

Patient	Age	Sex	Physical signs and symptoms	Size of gland to palpation	Av. pulse range	Av. blood pressure	Av. pulse pressure	Basal metabolic rate	Blood cholesterol (mg. per 100 ml.)	Peak galactose tolerance level (mg. per 100 ml.)*	Iodine therapy	Wt. change	Clinical diagnosis	Aspiration biopsy (cell height in microns)	Regular section (cell height in microns)	Diagnosis from aspiration biopsy	Diagnosis from regular section	Pathologic diagnosis
1. S. C.	59	M	Cardiac decomp., tremor	Large nodular	70–120	130/80	50	+54, +60	..	84	Yes	Loss	Toxic adenoma	9.5	8.8	T.N.G.†	T.N.G.†	Toxic adenoma
2. M. B.	28	F	Exophthalmus, cardiac murmur, sweats, tremor	Small	80–100	130/60	70	+68, +23	260	90	Yes	Loss	Diffuse toxic hyperthyroidism	8.1	8.3	T.D.G.	T.D.G.	Quiet phase, T.D.G.†
3. A. C.	33	F	Tremor, fatigue, palpitation, sweats	Large smooth	88–112	114/62	52	+62, +47 +39, +44	160	63	Yes	Loss	Diffuse toxic hyperthyroidism	9.2	9.5	T.D.G.	T.D.G.	T.D.G.
4. N. L.	57	F	Tremor, sweats, fibrillation, nervousness	Large smooth	90–110	188/80	108	+47, +43	..	..	Yes	Loss	Diffuse toxic hyperthyroidism	8.3	8.4	T.D.G.	T.D.G.	T.D.G., thyroiditis
5. E. P.	43	F	Tachycardia, tremor, muscle pains	Small	80–130	130/70	60	+46, +19	100	61	Yes	Loss	Diffuse toxic hyperthyroidism	10.5	10.1	T.D.G.	T.D.G.	Moderate hyperplasia
6. C. M.	28	F	Nervousness	Small subster.	95–115	120/60	60	+16, +29	..	83	Yes	Loss	Hyperthyroidism	9.7	9.0	T.N.G.	T.N.G.	Cystic hemor. adenoma
7. B. M.	60	M	Syst. murmur, spells, coma (diabetic, morphine addict)	Large nodular	80–105	135/70	65	+50, +47 +27, +24	130	..	Yes	Loss	Hyperthyroidism	7.8	8.0	N.T.N.G.	N.T.N.G.	Cystic hemor. adenoma
8. C. R.	58	F	Nervousness, tremor	Small	80–100	135/70	65	+42, +36	140	86	Yes	Loss	Toxic hyperthyroidism	8.7	8.4	T.D.G.	T.D.G.	T.D.G.
9. R. L.	34	F	Palpitation, nervousness	Small	80–110	145/80	65	+54, +33	..	90	Yes	Loss	Diffuse toxic hyperthyroidism	9.8	9.7	T.D.G.	T.D.G.	T.D.G.
10. C. L.	30	M	Sweats, nervousness	Small	95–120	130/75	55	+44, +30	..	74	Yes	Loss	Diffuse toxic hyperthyroidism	8.3	7.6	T.D.G.	T.D.G.	Moderate hyperplasia
11. J. M.	31	M	Nervousness	Large nodular	75–100	120/75	50	+35, +19	130	80	No	..	Toxic adenoma	8.4	8.5	T.N.G.	T.N.G.	Toxic adenoma
12. E. S.	44	M	Nervousness	Small	80–110	140/80	60	+34, +15	..	75	Yes	Loss	Hyperthyroidism	7.1	7.0	T.D.G.	T.D.G.	T.D.G.
13. E. C.	36	F	Exophthalmus	Small	85–120	140/85	55	+40, +28	..	80	No	..	Toxic adenoma	8.4	8.4	T.N.G.	T.N.G.	T. adenoma
14. S. T.	38	M	Sweats, nervousness	Large nodular	70–116	130/80	50	+56, +40	..	75	Yes	Loss	Toxic adenoma	8.7	8.8	T.N.G.	T.N.G.	T. adenoma
15. N. T.	57	M	Palpitation, sweats	Large smooth	90–110	116/62	54	+47, +38	110	61	Yes	Loss	Diffuse toxic hyperthyroidism	7.4	7.6	T.D.G.	T.D.G.	T.D.G., thyroiditis
16. F. R.	60	M	Fatigue, nervousness	Small nodular	95–115	128/64	64	+30, +25	100	65	No	..	Toxic adenoma	8.3	8.3	T.N.G.	T.N.G.	Toxic adenoma
17. H. W.	50	M	Palpitation	Small	84–96	120/70	50	+25, +18	..	54	No	..	Hyperthyroidism	7.8	8.0	T.D.G.	T.D.G.	T.D.G.

* Normal peak value of galactose tolerance is 30 or less in 1 hour.
† T.N.G. is toxic nodular goiter; T.D.G. is toxic diffuse goiter; N.T.N.G. is non-toxic nodular goiter.

nosis of toxicity was established. In 1, Case 7, the diagnosis of toxicity could not be established by aspiration biopsy. This patient was a diabetic and a narcotic addict which may explain some of the discrepancy.

The clinicians in charge of these cases used the basal metabolic rate, primarily for diagnosis, giving us, therefore, elevated B.M.R. readings in all cases. As we used only operated cases for these studies of aspiration biopsy we cannot draw a true comparison between the results of the 2 tests.

In 8 cases we obtained a blood cholesterol reading. Using a normal of 150 to 180 mg. per 100 cc., only 6 of the 8 were decreased enough to indicate a diagnosis of hyperthyroidism.

TABLE 2.—NORMAL CASES

	1	2	3
Patient	L. de F.	C. L.	G. W.
Age	24	22	25
Sex	M	M	M
Size of gland to palpation	Small	Small	Small
Average pulse range	65–80	75–82	70–80
Average blood pressure	104/80	120/80	120/82
Average pulse pressure	24	40	38
Basal metabolic rate	−2	+4	+2
Aspiration biopsy cell height, microns	6.7	6.3	5.3
Diagnosis as to function of thyroid gland from aspiration biopsy	Normal	Normal	Normal
Clinical diagnosis	Inguinal hernia	Postoperative appendectomy	Fractured femur

In 15 cases galactose tolerance tests were done. Using a normal peak value of galactose tolerance as 30 mg. per 100 cc. or less in 1 hour, we found that all 15 cases had readings indicating hyperthyroidism.

In all cases the presence of toxicity was confirmed by other clinical data and examination of surgical specimens in the ordinary manner.

Aspirations done on 3 normal cases likewise confirmed the accuracy of the test and helped confirm the standards for cell heights used as our criterion for diagnosis (Table 2). These aspirations again were of the magnitude expected. The average cell heights were all under 7 microns as would be expected in normal cases.

Summary and Conclusions. 1. A method has been described for obtaining aspiration biopsies of the thyroid gland.

2. Aspiration specimens from 20 thyroid glands were examined microscopically and 100 acinar cells measured from each. Surgical specimens from 17 of these glands were obtained and 100 acinar cells measured from each. These results were compared with each other and with clinical data.

3. It was found that a diagnosis of toxicity could be made on 16 of the first 17 aspiration specimens by the measurements alone. It was also found that measurements from the aspirations agreed very closely with those from the surgical specimens.

4. In the cases described, the measurement of acinar cell heights of thyroid aspiration specimens has confirmed the diagnosis of toxicity in a majority of cases. Though it is recognized that methods now

* Normal peak value of galactose tolerance in 30 or less in 1 hour.
† T.N.G. is toxic nodular goiter; T.D.G. is toxic diffuse goiter; N.T.N.G. is non-toxic nodular goiter.

17. H. W. 50 M Palpation

in use are often adequate to decide the matter of toxicity, it is hoped that this direct method may prove to be a valuable adjunct in the diagnosis of thyrotoxicosis.

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COLD HEMAGGLUTININS IN PRIMARY ATYPICAL PNEUMONIA AND OTHER RESPIRATORY INFECTIONS*†

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Until recently, autohemagglutination in man has been considered to be an unusual phenomenon, associated primarily with hepatic involvement or blood dyscrasias. In 1918, however, Clough and Richter[1] reported the finding of an autohemagglutinin in the serum of a case of bronchopneumonia. Their careful investigation revealed that the reaction depended solely on a peculiarity in the serum, occurred only in the cold, and was reversible at room temperature. The agglutinin was absorbed from the serum by the patient's cells and by human group O cells, as well as by cells of different species of animals. Although

* Presented by Norman L. Cressy, Major, M.C., A.U.S., at the meetings of the Society of American Bacteriologists, New York City, May 4, 1944.

† This investigation was supported through the Commission on Acute Respiratory Diseases, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Service, Office of the Surgeon General, United States Army, and by grants from the Commonwealth Fund, the W. K. Kellogg Foundation, the John and Mary R. Markle Foundation, and the International Health Division of the Rockefeller Foundation to the Board for the Investigation and Control of Influenza and Other Epidemic Diseases for the Commission on Acute Respiratory Diseases.

‡ Members and associates of the Commission on Acute Respiratory Diseases are: John H. Dingle, Major, M.C., A.U.S., Director; Theodore J. Abernethy, Major, M.C., A.U.S.; George F. Badger, Captain, M.C., A.U.S.; Joseph W. Beard, M.D.; Norman L. Cressy, Major, M.C., A.U.S.; A. E. Feller, M.D.; Irving Gordon, M.D.; Alexander D. Langmuir, Captain, M.C., A.U.S.; Charles H. Rammelkamp, Jr., M.D.; J. M. Ruegsegger, M.D. (resigned); Elias Strauss, Captain, M.C., A.U.S.; and Hugh Tatlock, 1st Lieutenant, M.C., A.U.S.

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the agglutinating activity of the serum decreased as the patient recovered, it did not completely disappear. The conclusion was reached that the phenomenon was an individual and probably hereditary peculiarity, and that the strength of the reaction may or may not have been related to the acute infection.

During the past year, Peterson, Ham and Finland[7] and others[6,8,9] have noted the presence of cold hemagglutinins in the serum of patients with primary atypical pneumonia. In retrospect, it seems likely that the patient studied by Clough and Richter suffered from atypical pneumonia, and that the hemagglutinin was in all probability related to that illness. Knowledge of the mechanism of cold hemagglutination, however, has not been extended beyond that derived from Clough and Richter's study, nor have sufficient data been accumulated regarding the extent of the reaction in respiratory diseases.

The purpose of this report is to present the results of a study of cold hemagglutination in 93 cases of primary atypical pneumonia and 121 cases of other types of respiratory disease.

Methods. *Selection of Patients.* All of the patients included in this study were soldiers admitted to the Station Hospital at Fort Bragg during the winter and spring of 1942–43. The diagnoses were made by members of the Commission on Acute Respiratory Diseases and were based on the criteria presented in a previous paper.[3] Patients were included in the study group if the diagnosis on admission was "probable atypical pneumonia," exudative tonsillitis, or exudative pharyngitis. Patients who had been ill for longer than 48 hours before coming under observation were admitted to the study only if the histories appeared to be reliable. Cases which were originally diagnosed as "probable atypical pneumonia" or exudative pharyngitis or tonsillitis, but did not eventually prove to be such, were kept in the series and studied in the same manner as the other patients. The final diagnosis and the number of cases in each category are listed in Table 1.

TABLE 1.—DISTRIBUTION OF 214 CASES BY DIAGNOSIS AND MAXIMUM COLD HEMAGGLUTININ TITER

Diagnosis	Maximum titer											
	<8	8	16	32	64	128	256	512	1024	2048	>2048	Total
Atypical pneumonia	42	8	7	7	5	4	4	7	3	4	2	93
Pneumococcal pneumonia	2	2										4
Bronchitis resembling atypical pneumonia	8	2		1								11
Sinusitis	1											1
Exudative pharyngitis and/or tonsillitis	62	22	4	5		1						94
Scarlet fever	3		1									4
Measles	2		1									3
Undifferentiated	4											4

Figures in table indicate number of cases

Handling of Serum Specimens. Blood was taken from each patient when first seen, and thereafter 2 or 3 times weekly for the duration of his hospital stay. In most instances the final blood was taken about 1 month following onset of illness.

The blood was allowed to clot overnight at room temperature before the serum was removed. The serum was then stored in rubber-capped sterile bottles at 4° C. until used.

Technique of Test. All of the sera from each patient were tested on the same day. Human defibrinated Group O erythrocytes were obtained daily from the same donor for all tests. The cells were washed three times with approximately equal volumes of buffered physiologic saline[4] and then packed in the horizontal centrifuge at 1500 r.p.m. for 15 minutes. A 0.2% suspension of packed cells in buffered physiologic saline was used in the test.

Two-fold serial dilutions of the sera beginning with a 1–4 dilution were made in buffered physiologic saline in 0.5 ml. volumes. To each of these was added an equal volume of 0.2% suspension; the final dilution of serum in the first tube was 1–8. After thorough shaking, the racks were kept at approximately 4° C. overnight. On the following morning the tests were removed from the refrigerator one rack at a time and read immediately before warming could occur. A fluorescent source of light and a black background were used. Readings were graded from 4+, which consisted of a tight disk of cells which did not break up readily on gentle shaking of the tube, to 1+, which was the least amount of definite clumping of cells visible to the unaided eye. The end-point was taken as the highest dilution in which definite agglutination occurred. Positive tests were reread after 30 minutes at room temperature to eliminate hetero-agglutinins or other antibodies as the cause of agglutination. All titers mentioned are final dilutions of serum and are expressed as the reciprocal of that dilution.

Positive sera of previously determined titer were included in each day's tests as a check on the sensitivity of the tests from day to day. In no instance did these control sera vary more than ± 1 dilution on repeated tests.

Results. *Effect of Variations in Technique.* The above outlined method was the final form of the test employed in this study. Before it was adopted, however, 317 sera were tested using the method described by Ham,[5] in which a 2% suspension of cells was used. The change to an 0.2% suspension was made in the hope of increasing the sensitivity of the test. The results using the two concentrations of cells are compared in Table 2. With but 4 exceptions the titers were higher using the 0.2% suspension, and 59 sera which had been considered to have titers less than 8 using the 2% cell method, were found to have titers ranging from 8 to 256.

TABLE 2.—COMPARISON OF RESULTS OF COLD HEMAGGLUTININ TITERS OBTAINED ON 317 SERA USING TWO DIFFERENT CONCENTRATIONS OF CELLS

	Titer using 0.2% cells							
Titer using 2% cells	<8	8	16	32	64	128	256	512
<8	238	27	11	9	3	7	2	
8	1	..	..	2	2	2	1	
16	..	..	1	1	1	1	..	
32	..	..	..	..	..	..	..	1
64	..	..	..	1	..	1	2	..
128	..	..	..	..	..	..	1	1
256	..	..	..	..	..	..	1	..
512	..	..	..	..	..	..	..	..

Figures in table indicate number of cases

The age of the erythrocytes was also found to be a factor in the results (Fig. 1). Nine sera were tested daily for from 4 to 6 days using cells taken from a donor on the 1st day of the experiment. The results are shown by the solid lines in Figure 1. In two sera (A and B) in which the maximum titer was 32, the titer fell to less than 8 when the cells used reached the age of 3 and 4 days respectively. The titer of one other serum (I), the maximum titer of which was 64, fell to less than 8 on the 6th day. The titer of serum C showed a drop of 3 tubes on the 5th day and serum G showed a drop of 2 tubes on the 4th and 6th days. Thus in 5 of the 9 sera tested there was a drop of 2 or more tubes in those tests using cells which were 3 or more days old. In contrast to this is the fact that the same sera when tested with

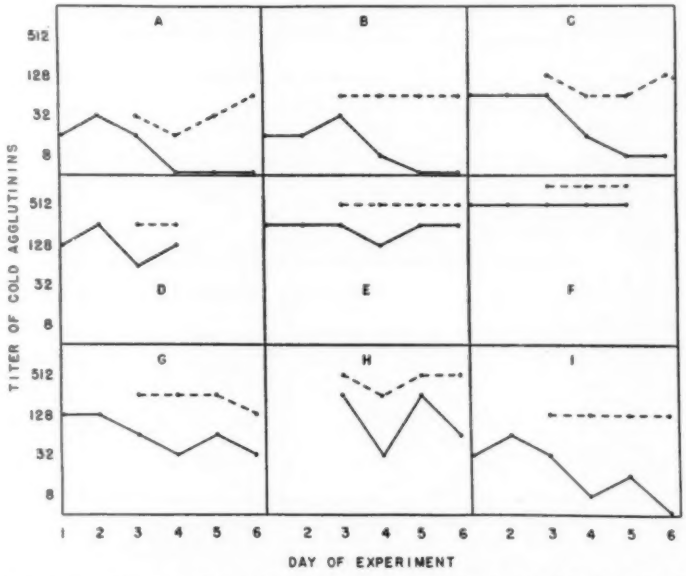

FIG. 1.—Comparison of cold agglutinin titers using cells obtained fresh daily (broken lines) and cells obtained on the first day and used throughout the experiment (solid lines).

fresh cells daily (broken line, Fig. 1) showed no tendency to a progressive decrease in titer, and the maximum variation was 2 tubes. In every instance, the tests performed with the fresh cells showed a much more definite and more easily read agglutination than did the same tests carried out with old cells.

In an attempt to evaluate possible differences in the agglutination of cells from different Group O donors, cells were obtained from 4 different donors and tested with 6 sera. There were no variations of more than 1 dilution in the titers.

Analysis of Cases. The results of the studies were analyzed for the purpose of determining the following points: (1) The titer of cold agglutinins in atypical pneumonia and other respiratory infection;

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(2) the titer of cold agglutinins throughout the course of illness and convalescence; (3) the relationship of cold agglutinins to the severity of illness.

The Titer of Cold Agglutinins in Atypical Pneumonia and Other Respiratory Infections. Table 1 presents the maximum titers of cold agglutinins obtained during the illness in 93 cases of atypical pneumonia and 121 cases of other respiratory infections. The sera of 42 cases of atypical pneumonia had titers lower than 8. The remainder (51) had titers varying from 8 to more than 2048. In contrast, the titers for other respiratory infections studied range only from 8 to 32 with one exception. This single exception occurred in a patient ill with acute exudative pharyngitis. The maximum titer for cold

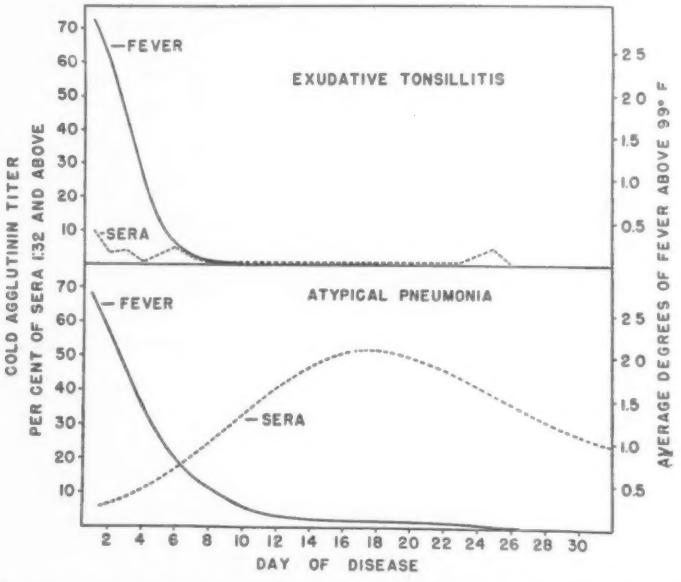


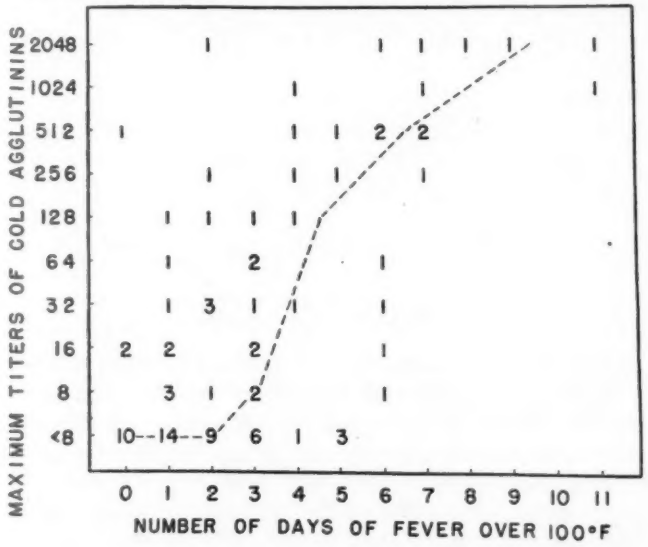
FIG. 2.—Percentage of sera from cases with atypical pneumonia and cases with exudative pharyngitis showing titers of 32 or more and average degrees of fever above 99° F. by day of disease.

agglutinins, which was 128, was found in the specimen obtained the day after the onset of his illness. Subsequent titers on specimens 4 days and 3 weeks later were 32 and 16, respectively. A Group A, non-typable, beta-hemolytic streptococcus was isolated from pharyngeal cultures, but the sera did not show a rise in antistreptolysin titer. There was no history of a recent antecedent respiratory infection. The explanation for the presence of cold agglutinins in this patient is not apparent.

Titer of Cold Agglutinins Throughout the Course of Illness and Convalescence. Figure 2 shows the per cent of sera from patients with atypical pneumonia and patients with exudative tonsillitis which had a titer of 32 or more by day of disease and compares this with the

average degrees of fever above 99° F. for each day. These data are based on 49 cases of atypical pneumonia and 85 cases of tonsillitis in which it was felt that the date of onset could be determined accurately. In the cases with atypical pneumonia the per cent of sera with a titer of 32 or more increased from 6% in the 1st week to 50% in the 3rd week of illness, at which time, if one considers the termperature curve as an index, the patients were well past the acute phase of their illness. The results in 85 cases of acute pharyngitis provide a distinct contrast when charted in the same manner. Ten % of the sera taken on the 1st day of illness showed a titer of 32 or more. Thereafter the incidence was never found to be above 5%.

TABLE 3.—DISTRIBUTION OF 89 CASES OF ATYPICAL PNEUMONIA BY NUMBER OF DAYS OF FEVER OVER 100° F. AND MAXIMUM TITER OF COLD AGGLUTININS



Relationship of Cold Agglutinins to Severity of Illness. Two objective criteria which lent themselves readily to reasonably accurate measurement were chosen as indices of severity of illness. These were the number of days of fever above 100° F. and the extent of the pulmonary lesion as evaluated by roentgenogram and physical examination.

Table 3 presents a correlation between the number of days of fever over 100° F. and the maximum titer of cold agglutinins at any time during the course of illness. The titer rose sharply between the 2nd and 10th days of fever. In general, the more days of fever which the patients experienced, the higher the cold agglutinin titer became. None of the cases with fever over 100° F. for 7 days or more had a titer lower than 256.

The relationship between the maximum titer of cold agglutinins and the amount of pulmonary involvement is shown in Table 4. Of

69 cases with single lobe lesions 22 or 32% had a titer of 32 or more, while of 18 cases with multiple lobe lesions 13 or 72% had a titer of 32 or more. There were 10 cases in which upper lobe lesions occurred either singly or in combination with involvement of other lobes. One of the 10 had a titer of less than 8; one had a maximum titer of 16, and the remaining 8 (80%) had titers of 32 or more. The highest titer seen in the entire series (65,536) had involvement of all three lobes of the right lung. The 3 cases with involvement of 1 upper lobe alone had titers of 8, 16, and 512.

TABLE 4.—DISTRIBUTION OF CASES OF ATYPICAL PNEUMONIA ACCORDING TO MAXIMUM TITER OF COLD HEMAGGLUTININS AND NUMBER OF LOBES OF THE LUNG INVOLVED

No. of lobes involved	Maximum titer cold agglutinins											
	<8	8	16	32	64	128	256	512	1024	2048	>2048	Total
1	37	5	5	5	4	3	2	4	2	2		69
2	2		2	1	1	1	2		1	2		12
3	1							3			1	5
4												
5										1		1

Figures in table indicate number of cases

It has recently been suggested by Dameshek[2] that the production of cold agglutinins might be influenced by the administration of sulfonamides. Sixty of the cases in this series are known to have received no sulfonamides during the course of their hospitalization. The titers in these cases ranged from less than 8 to 2048. Only 10 cases were treated with sulfonamides and the range of cold agglutinin titers was exactly the same as in the non-treated cases.

Discussion. During the last year numerous reports have appeared in the literature concerning the occurrence and significance of cold agglutinins in the sera of patients with primary atypical pneumonia. Peterson, Ham and Finland[7] indicated that the presence of cold agglutinins might be of value in the differential diagnosis of this disease. They found that the highest titers occurred at or near the end of the febrile period. Horstmann and Tatlock[6] confirmed these observations, and stated that they were unable to demonstrate a clear-cut correlation between the severity of the illness and the titer of cold agglutinins.

In the present series only 55% of the cases were found to have cold agglutinins and only 31% had titers of a level sufficiently high to distinguish them from other respiratory infections. Turner[8] has reported a series from England of 22 cases of atypical pneumonia and 24 cases of other infectious diseases. Approximately 50% of the cases of atypical pneumonia in this series had titers of more than 16, whereas none of the other diseases had titers greater than 16. More

recently, Turner and others[9] reported the results of a somewhat larger series of cases. They found that of 83 cases of atypical pneumonia, 50% had titers of at least 32 and 28% had titers of 128 or more. Of 136 cases of other types of disease including "influenza or grippe," undifferentiated upper respiratory infection, pulmonary tuberculosis and mumps, the titer was over 16 in only 4 cases and in no instance was it over 64.

The results reported here are in close agreement with regard to the percentage of positive titers with those of Turner and his co-workers[4,5] but differ considerably from those of Peterson, Ham and Finland,[7] and Horstmann and Tatlock,[6] who reported that a large majority of their patients developed cold agglutinins. This may well be attributable to the fact that the present series and that of Turner *et al.* were both based on patients in military hospitals who, in general, may be less severely ill than patients admitted to civilian institutions. The data presented in Tables 3 and 4 suggest strongly that the height of the titer of cold agglutinins is related to the severity of the illness.

The data presented in Table 2 indicate that a titer of 64 or more in a patient ill with respiratory infection is strong evidence in favor of a diagnosis of atypical pneumonia. Lower titers are also of value, especially if sera taken at intervals during the course of illness show a rise in titer in early convalescence, and a drop thereafter. For example, in 93 cases of atypical pneumonia, there were only 8 cases with maximal titers of 32 or more which did not show this picture. The illnesses of 6 of these were of indefinite onset; in one a maximum titer was found 9 days after onset. In the 8th case, the maximum titer was found on the day after the estimated onset of atypical pneumonia. In this instance, however, the true onset was difficult to determine because of a mild respiratory infection which began 8 days earlier.

If the absolute level of titers is to be considered of value, it is important to know something of the limitations of the test used and the possible sources of error which may influence the results. Evidence has been presented to show that the age of the red cells used influences the sensitivity of the test. There is the further possibility that the test is subject to a certain amount of error because of possible variation in the agglutinating qualities of the donor's cells from day to day. It would appear from the data thus far obtained that variations in titer of one dilution in either direction may be expected with the methods employed.

Summary. 1. A modified method for detecting cold agglutinins in serum has been described.

2. A study of the occurrence of cold agglutinins in the sera of 93 cases of atypical pneumonia and 121 cases of other types of respiratory diseases has been presented and their value in diagnosis discussed.

3. In this series the titer of cold agglutinins was found to be proportional to the severity of the illness as measured by the number of days of fever and the extent of the pulmonary lesion.

The Commission on Acute Respiratory Diseases takes pleasure in acknowledging the assistance of the technical staff of the laboratory: Marguerite Buckingham, Walter A. Mickle, Jr., Barbara Mulliken, Thomas J. Oliver, 1st Lieut., Sn.C., Ralph L. Robinson, 2nd Lieut., Sn.C., and Edith E. Searles.

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THE CONCOMITANT ADMINISTRATION OF SULFATHIAZOLE AND QUININE OR ATABRINE*

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In 1941 Harned and Cole[2] observed in rats that the concomitant administration of quinine and sulfapyridine increased the absorption of sulfapyridine from the intestine and also the percentage and total amount of the acetylated fraction in the urine. The largest dose of quinine used in their series produced an average increase of 96% in the excretion of acetylsulfapyridine. Since this effect was not accompanied by an increase in the volume of the urine, the possibility of renal damage suggested that these drugs should be considered, to an appreciable degree, therapeutically incompatible in the rat. The close relationship between the behavior of the sulfonamides in this species and in man inevitably raised the question of the existence in the human of similar incompatibilities. In malarial districts the frequent necessity for the concurrent administration of antimalarials and sulfonamides would appear to demand that the question be answered by observations on man, and because generalizations in this field are hazardous, conclusions drawn must be confined to the results from a specific combination of drugs.

The rather short life of sulfapyridine in therapeutics precluded its use in our human experiments. In its place sulfathiazole was sub-

* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Woman's Medical College of Pennsylvania.

stituted. It is the purpose of this paper to report data on the concomitant administration of sulfathiazole and quinine or atabrine to 99 volunteer, hospitalized patients.

TABLE 1.—THE SCHEDULE OF DOSES

The sulfathiazole was given in 0.500-gm. tablets, the quinine bisulfate in 0.324-gm. capsules, the atabrine in 0.100-gm. tablets. When two drugs were administered on the same day a dose of each was always given at 8 A.M.

Drug-Group 1.	*Sulfathiazole:* 3 gm. daily for 7 days; 2 gm. initially followed at intervals of 8 hours by doses of 1 gm.
	Quinine bisulfate: 1 gm. daily on days number 5, 6 and 7; 0.324 gm. per dose administered with the sulfathiazole.
Drug-Group 2.	*Sulfathiazole:* the same as in Group 1.
	Quinine bisulfate: 1 gm. daily for the first 4 days; 0.324 gm. per dose administered with the sulfathiazole.
Drug-Group 3.	*Sulfathiazole:* the same as in Group 1.
	**Quinine bisulfate:* 2 gm. daily for 7 days; 0.324 gm. per dose at intervals of 4 hours.
Drug-Group 4.	*Sulfathiazole:* 4 gm. daily for 7 days; 2 gm. initially followed at intervals of 6 hours by doses of 1 gm.
	**Quinine bisulfate:* the same as in Group 3.
Drug-Group 5.	*Sulfathiazole:* 6 gm. daily for 7 days; 2 gm. initially followed at intervals of 4 hours by doses of 1 gm.
	**Quinine bisulfate:* the same as in Group 3.
Drug-Group 6.	*Sulfathiazole:* 6 gm. daily for 6 days; the same schedule as in Group 5.
	Atabrine: 0.300 gm. daily for 5 consecutive days; 0.100 gm. per dose at intervals of 8 hours. The administration of the atabrine started 24 hours before the first dose of sulfathiazole.
Drug-Group 7.	*Sulfathiazole:* the same as in Group 5. No antimalarial.

* In addition to the dosage recorded, 1 gm of quinine bisulfate divided into 3 equal doses was given during the 18 hours which immediately preceded the first dose of sulfathiazole.

Method. Of 76 patients who completed the experimental period, 9 were not included in the tables because they represented transitional doses of drugs or deviations from the adopted routines. The data on 67 subjects are recorded and analyzed. These were divided, according to the drugs and the daily doses, into 7 groups, Table 1. In general, the schedule called for the administration of sulfathiazole in daily doses ranging from 3 to 6 gm. for a period of 7 days. The daily dose of quinine varied from 1 to 2 gm. in the different groups and was administered during the last 3 days of the sulfathiazole-period in Group 1, during the first 4 days of the sulfathiazole-period in Group 2, and for 1 day preceding the sulfathiazole and then concomitantly with the sulfonamide for 7 days in Groups 3, 4, and 5. Atabrine was used in only one dose, 0.3 gm. per day for 5 days, and this drug was started 24 hours before the first dose of sulfathiazole (Group 6). A control group received only sulfathiazole for 7 days (Group 7). The first dose of sulfathiazole was given at 8 A.M. From this time throughout the experimental period, 24-hour specimens of urine were collected and analyzed quantitatively for free and total sulfathiazole. Each sample was examined microscopically for casts, cells and crystals. The specific gravity was determined and qualitative tests for albumin and sugar were made. If a patient discarded a specimen or vomited he was dropped from the experiment.

Twenty-eight hours after the first dose of sulfathiazole and at intervals of 48 hours thereafter, samples of blood were analyzed for free and total sulfathiazole, hemoglobin, and the total number of W.B.C. The method of

Bratton and Marshall[1] was used for the determination of sulfathiazole on filtrates of blood which represented a dilution of 1:100. Hemoglobin was determined by the Newcomer method.[3] All colorimetric readings were made with a photoelectric colorimeter.

TABLE 2.—DIAGNOSES IN PATIENTS WHO COMPLETED EXPERIMENTAL PERIOD

Drug-Group Number: / Mean age:	1 47	2 47	3 38	4 48	5 48	6 39	7 35	Total
Congestive heart failure	5	4	4	8	10		3	34
Inguinal hernia						6	2	8
Acute appendicitis						4	2	6
Lobar pneumonia	1		1		1			3
Amputation of both feet						1*	1*	2
Acute arsenic poisoning							1	1
Carcinoma of stomach			1					1
Incisional hernia							1	1
Head injury					1			1
Hodgkin's disease	1							1
Body and limb lacerations						1		1
Lung abscess				1				1
Pleural effusion					1			1
Neuritis			1					1
Trigeminal neuralgia			1					1
Pulmonary tuberculosis				1				1
Tuberculous lymphadenitis			1					1
Sciatica	1							1
Meningovascular syphilis					1			1
Total	8	4	9	10	14	12	10	67

* Same patient.

Subjects. Fifty % of the subjects were partially stabilized cardiac cases. Twenty % were surgical cases operated upon for hernia or appendicitis. The remaining patients were hospitalized for a wide variety of conditions, only 1 of which would have been expected to have yielded aberrant results. This was a convalescent case of acute arsenic poisoning, but the data on this patient were consistent with those of the other members of the group. Table 2 lists the diagnoses and mean ages of the patients in the 7 drug-groups studied.

Unfavorable Reactions. The patients were watched closely for subjective and objective evidence of toxicity. Of the 99 patients in the series, 5 were dropped for a lapse in coöperation, 1 undiagnosed case

was discontinued when there was no response to the experimental therapy, and 17 were abandoned because of unfavorable reactions to the drugs. Seventy % of the reactions consisted of vomiting, but most of these patients would have been continued had we not been interested in the quantitative relations between the intake and output of sulfathiazole. Vomiting appeared in each of the last 5 drug-groups, but the incidence in the groups which received sulfathiazole and quinine was about twice that in the groups administered sulfathiazole alone and with atabrine. The interpretation of this difference is complicated by the fact that the sulfathiazole-quinine groups contained a higher percentage of cardiac cases, and it is possible that the reaction might have been associated with changes in the heart produced by quinine or digitalis. The other unfavorable reactions were: mental confusion in 1 patient in Group 5; unexplained chills in 1 patient in Group 5; drug fever in 1 patient in Group 7; and hematuria in another patient in Group 7. This patient had a urine volume of 2400 cc. on the first day and 1890 cc. on the second day. The hematuria developed during the second day. Recurrent epistaxis was observed in 1 patient, in a transitional drug-group, who was receiving daily 6 gm. of sulfathiazole and 1 gm. of quinine bisulfate.

TABLE 3.—BLOOD SULFATHIAZOLE

Drug-Group	Hours subsequent to the first dose of sulfathiazole: 28 — No. of patients	Sulfathiazole: Free mg. %	Free S.E.m ±	Total mg. %	Total S.E.m ±	Free %	76 — No. of patients	Sulfathiazole: Free mg. %	Free S.E.m ±	Total mg. %	Total S.E.m ±	Free %
1	8	3.2	0.14	5.5	0.42	57.7	8	2.5	0.39	3.8	0.51	66.5
2	4	2.9	0.26	4.2	0.17	69.4	4	3.3	0.22	4.9	0.39	66.6
3	9	2.6	0.36	3.4	0.42	78.0	9	4.0	0.30	5.5	0.48	73.4
4	10	3.7	0.49	5.0	0.67	75.0	10	4.0	0.70	5.6	0.99	71.6
5	14	5.1	0.65	6.5	0.63	77.9	13	4.5	0.64	6.9	0.74	64.2
6	12	5.4	0.26	6.6	0.34	82.0	12	4.9	0.27	6.2	0.26	78.4
7	10	5.3	0.59	6.8	0.61	78.4	10	4.9	0.40	7.4	0.35	66.2
	Hours subsequent to the first dose of sulfathiazole: 124						148					
1	7	3.1	0.41	5.1	0.63	60.8	1	4.1	....	7.8	....	52.6
2	3	3.3	0.90	5.2	0.85	63.7	1	4.3	....	6.4	....	67.2
3	9	3.4	0.47	4.8	0.60	71.6	..	...	....	...	....	....
4	10	4.3	0.39	5.5	0.50	77.6	..	...	....	...	....	....
5	10	5.1	0.43	7.3	0.70	69.0	3	4.7	....	6.6	....	74.1
6	4	4.6	0.48	5.2	0.82	89.3	10	5.1	0.37	5.9	0.51	86.5
7	10	6.3	0.55	7.8	0.89	80.8	..	...	....	...	....	....

Results on Blood and Urine. Blood. Neither the hemoglobin nor the number of W.B.C. was affected unfavorably by any of the drug-combinations used. The sulfathiazole levels are recorded in Table 3. Neither quinine nor atabrine influenced significantly the free or the total sulfathiazole in any of the groups.

Urine. An inspection of Groups 1, 2 and 3 in which we have a combination of small doses of sulfathiazole with small and large doses of quinine reveals no effect of the latter drug on the total excretion of sulfathiazole or on the percentage excreted free (Table 4). However, when the dose of sulfathiazole was 6 gm. per day, quinine in daily doses of 2 gm. depressed the daily total excretion of sulfathiazole. The mean depression for the 7-day period of the ratio $\frac{\text{urinary sulfathiazole}}{\text{administered sulfathiazole}}$ amounted to 15%. Although the volume of urine in the group which received sulfathiazole alone averaged for the period more than that

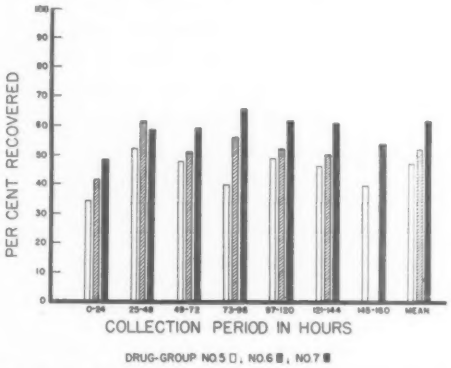

FIG. 1.—The effect of quinine and atabrine on the percentage of the administered sulfathiazole recovered in the urine. Drug-Group No. 5 received quinine and sulfathiazole; No. 6, atabrine and sulfathiazole; and No. 7, sulfathiazole alone. The dose of sulfathiazole was the same in each group. The complete schedule of drugs and the number of patients in each group are recorded in Tables 1 and 2.

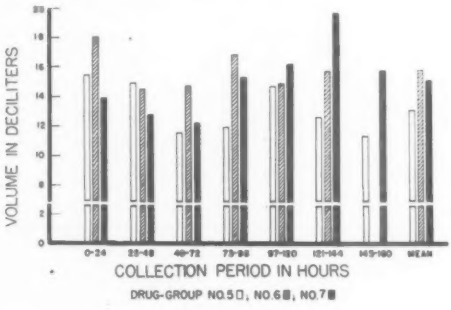

FIG. 2.—Urine volumes.

of the group administered the 2 drugs, the correlation between the urinary volume and the total amount of sulfathiazole in the urine is poor (Figs. 1 and 2). For most of the periods the concentration of sulfathiazole in the urine of the group administered quinine (No. 5) was less than in the control group (No. 7). It is also interesting to note that the percentage of urinary sulfathiazole excreted free is a little less in the quinine-group. This difference is not statistically significant, and as an isolated observation it would be unworthy of notice, but the same trend was observed in the results on blood.

TABLE 4.—SULFATHIAZOLE EXCRETED IN URINE

Hours subsequent to the first dose of sulfathiazole

Drug-Group	No. of patients	0–24						25–48						49–72					
		Sulfathiazole				Urine volume		Sulfathiazole				Urine volume		Sulfathiazole				Urine volume	
		Free		Total				Free		Total				Free		Total			
			S.E.$_M$		S.E.$_M$		S.E.$_M$		S.E.$_M$		S.E.$_M$		S.E.$_M$		S.E.$_M$		S.E.$_M$		S.E.$_M$
		mg.	±	mg.	±	cc.	±	mg.	±	mg.	±	cc.	±	mg.	±	mg.	±	cc.	±
1	8	1283	195	1836	311	871	186	1802	262	2435	294	1300	207	1205	214	1840	283	1391	215
2	4	2102	352	2572	362	2527	314	1687	207	2257	238	1720	275	1556	121	2063	113	1650	279
3	9	1622	174	1852	212	1984	298	1721	171	2133	159	2270	177	1513	121	1979	150	1690	216
4	10	1280	171	1676	211	1025	234	1641	281	2029	308	811	126	1504	325	1893	349	868	159
5	14	2090	238	2399	271	1532	202	2771	432	3133	469	1480	191	2591	441	2871	482	1155	153
6	12	2685	169	2903	183	1795	147	3435	150	3704	160	1445	161	2785	185	3090	189	1468	186
7	10	3096	299	3416	346	1382	151	3258	304	3527	314	1274	148	3340	213	3550	227	1212	130
		73–96						97–120						121–144					
1	8	1311	209	1976	278	1509	141	1431	220	2285	320	1505	209	1676	506	2307	588	1065	148
2	4	1760	187	2522	205	1947	296	1991	278	2719	350	1970	483	1667	128	2242	125	1915	143
3	9	1728	237	1937	206	1688	240	1583	278	2293	426	1748	512	1534	131	1886	118	1492	232
4	10	1659	294	2380	268	1032	188	1720	366	2227	366	1250	267	1466	228	1860	261	790	181
5	14	2099	276	2399	318	1187	186	2489	312	2950	365	1463	271	2545	549	2797	551	1263	212
6	12	3307	218	3382	219	1683	161	3031	220	3141	207	1483	157	2877	187	3024	209	1571	105
7	10	3734	251	3957	277	1531	149	3409	301	3716	312	1619	139	3475	224	3661	213	1977	263
		145–168																	
1	8	1267	239	1706	287	1043	184												
2	4	1719	103	2150	102	1675	246												
3	9	1343	129	1814	101	1750	162												
4	10	1436	286	1816	330	982	298												
5	14	2176	261	2384	315	1133	188												
6	12																		
7	10	3043	223	3244	251	1574	141												

Atabrine depressed the ratio, $\frac{\text{urinary sulfathiazole}}{\text{administered sulfathiazole}}$, to approximately the same extent as did quinine. In the atabrine-group the depression bore no relation to the urinary volume (Figs. 1 and 2). The percentage of free sulfathiazole in the urine was slightly greater in the atabrine group (No. 6) than in the control group (No. 7) and a similar tendency existed in the blood.

Summary and Conclusions. 1. The results obtained from 99 volunteer, hospitalized subjects indicate that the incidence of unfavorable reactions, with the possible exception of vomiting, is not increased by the concomitant administration of sulfathiazole and quinine or atabrine. The highest doses studied were: 6 gm. of sulfathiazole daily for 7 days; 2 gm. of quinine bisulfate for the same period; and 0.3 gm. of atabrine daily for 5 days.

2. The combination of drugs produced no detectible changes in the amount of hemoglobin or the total W.B.C. count.

3. Quinine and atabrine produced only minor changes in the free and total sulfathiazole in the blood and in the urine.

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THE EFFECT OF QUINIDINE ON THE MORTALITY OF RATS WITH EXPERIMENTAL MYOCARDIAL INJURY*

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The action of quinidine on the normal heart has been the subject of considerable investigation by pharmacologists, and there seems to be general agreement that the chief effects are prolongation of the refractory period, slowing of conduction time, and decrease in contractility. Large doses may cause either auriculoventricular block or even sino-auricular block, while still larger doses may induce complete arrest or ventricular fibrillation. All of these effects are probably due to one fundamental action, namely, the decrease in the restorative metabolism of the heart as has been emphasized by Goodman and Gilman.[2] The paradoxical relationship between ventricular fibrillation and quinidine action, the latter tending at times to prevent and at times to produce the former, can probably be ascribed, as Smith, McEachern and Hall[3] have pointed out, to the antagonistic effects of the action on conduction and on the refractory period. When the

* Aided by a grant from the Dazian Foundation for Medical Research.

prolongation of the latter predominates the tendency toward ectopic rhythms is reduced. On the other hand, when the delay in conduction time predominates favorable conditions are set up for circus movements.

When we pass from the normal heart to a consideration of the abnormal heart there is less unanimity of opinion concerning the action of quinidine. The effects of the drug apparently depend a great deal on the state of the heart at the time it is given. Thus, Smith and Boland[9] have pointed out that the drug causes sinus slowing in anesthetized animals and sinus acceleration in unanesthetized animals. Similarly, the prolongation of the P–R interval is much more striking in the presence of anesthesia, although the delay in intraventricular conduction occurs irrespective of anesthesia. The confusion which exists as regards the pharmacology of quinidine in abnormal hearts is reflected in the clinical literature. Most authors agree that the drug may be invaluable in the patients with ventricular tachycardia, but there is still considerable uncertainty concerning the indications and contraindications for it in patients with auricular fibrillation and in individuals who have a condition which is likely to lead to ventricular fibrillation. The suggestion has been made[4,10] that the drug should be used routinely in patients with coronary thrombosis, in an attempt to prevent ventricular fibrillation and sudden death. This suggestion has received certain support from the experiments of Wegria and Nickerson,[12] who have studied the susceptibility of the hearts of dogs to ventricular fibrillation induced by electric shocks of various strengths. They found that in these animals quinidine reduced susceptibility to ventricular fibrillation, but only provided the dose of quinidine was not too large and provided it was administered slowly. When large doses were administered rapidly, the susceptibility to induce fibrillation increased and spontaneous ventricular fibrillation frequently occurred.

In order to simulate more closely in experimental animals conditions that occur in patients, certain investigators have studied the effect of quinidine in dogs following the ligation of a coronary artery. Mousset de Espanes[5] observed no effect from quinidine in reducing the liability to ventricular fibrillation following such experimental coronary occlusion. On the other hand, Smith, McEachern and Hall[8] reported opposite results. They produced occlusion of a large coronary branch in conscious dogs and observed that, although the animals receiving the drug were susceptible to ventricular premature beats and ventricular tachycardia, they exhibited a diminished tendency—as compared to the controls—toward the development of fatal ventricular fibrillation. The mortality in their experiments was 55% in the animals receiving quinidine as compared to 75% in the control group. However, only a relatively small series of animals was used.

One finding of especial interest, reported by Smith, McEachern and Hall[8] was that in conscious dogs the administration of quinidine seemed to reduce the pain caused by occlusion of a coronary artery. This is in keeping with the observations of Proger and Minnich,[6] and of

Riseman and Brown,[7] who found that the amount of exercise required to induce anginal attacks was increased by the administration of quinidine. It would seem that these interesting observations merit further investigation.

The problem as to the possible value of quinidine in preventing ventricular fibrillation in patients predisposed to it can only be solved by the study of a large series of well-controlled cases. In view of the variability of the response of different individuals to the drug, it seems likely that such an investigation would necessarily involve several hundred patients. Consideration of the expense involved in experiments on many scores of dogs likewise make it difficult to arrive at an answer in these animals. Consequently, we have chosen to attack the problem in rats, which offer the advantage of making it feasible to carry out investigations on a large number of animals at a relatively slight expense. The rat, however, suffers from the disadvantage that one cannot readily induce a condition strictly comparable to coronary thrombosis in man.

Experimental Procedure. All experiments were carried out on rats of either sex weighing approximately 200 gm. The animals were obtained from our own colony, which is a mixture of the Wistar and several other strains. Myocardial injury was induced by burning the ventricular surface of the temporarily exteriorized heart, according to the technique described by us elsewhere.[11] The amount of tissue injured was kept reasonably constant in the different rats, and hence it is believed that the degree of injury produced in the animals treated with quinidine is quite comparable to that in the controls.

In one series of animals, quinidine was administered intraperitoneally immediately prior to the operative procedure. Another and larger group of animals received the initial injection of quinidine at the conclusion of the operation. The dose of quinidine employed varied from 0.005 to 0.002 gm. in different experiments. At the conclusion of the operation the animals which had received quinidine were placed in a cage which contained food to which quinidine had been added in such amount that each animal consumed approximately 0.02 gm. of quinidine per day. The control animals were treated similarly except that they received no quinidine at any time. The treated animals received the drug in the amount stated for a period of 3 weeks, at which time therapy was discontinued, as it was learned from experience that after this time all surviving rats remained in good condition except for an occasional one which would die of intercurrent disease.

The animals were observed at frequent intervals during the first few hours after the operation, and daily thereafter. Postmortem examinations were made in an attempt to determine whether death was the result of hemorrhage from the heart, infection in the chest, intercurrent disease such as pneumonia, or was unexplained. We were naturally particularly interested in those animals which displayed unexplained death, for it might reasonably be assumed that in these the development of cardiac irregularities such as ventricular arrest or ventricular fibrillation was concerned in the production of death.

Results. *The Operative Procedure.* Arrhythmias developed in most of the rats. The one most commonly observed was a sudden bradycardia which occurred in many of the animals when the heart was exteriorized. While the surface of the ventricle was being seared, sudden tachycardia of apparently ventricular origin (electrocardiograms were not taken) occurred in many of the animals. Ventricular fibrillation, lasting only 1 to 3 seconds occurred in about one-half of

them and was followed in each instance by prompt recovery. An attempt was made to estimate the comparative frequency and severity of these arrhythmias in the rats receiving quinidine, as compared to the controls. No significant difference was noted. No observations were made concerning arrhythmias after the chest had been closed.

The operative procedure resulted in severe respiratory distress. The animals had to be first anesthetized deeply with ether before the chest could be opened. The procedures of opening the chest, exteriorizing the heart, searing the surface of the ventricles, replacing the heart in the chest, and closing the chest ordinarily required a period of 30 seconds to 2 minutes, during which respiration was almost totally ineffective. Consequently, many of the animals developed respiratory failure and did not breathe spontaneously when the chest was closed. Artificial respiration was given both by inflating the lungs through a tube placed tightly over the nose and mouth of the animal, and by pressure on the chest wall. Even so, a number of the rats could not be made to breathe following the operative procedure. The incidence of such respiratory failure was much higher in animals receiving quinidine than in the controls. This point will be emphasized in more detail later.

TABLE 1.—EFFECT OF PREOPERATIVE AND POSTOPERATIVE ADMINISTRATION OF QUINIDINE ON MORTALITY CAUSED BY BURNING THE MYOCARDIUM

Group		No. of animals	Operative deaths*	Postoperative deaths†	Deaths during 1st wk. (2nd to 7th day)	Deaths during 2nd and 3rd wks.	Survivors (after 3 wks.)	Mortality (%)‡	Remarks
I	Controls	30	3	4	7	0	16	40.7	Quinidine administered prior to operation
	Treated¶	30	2	12	4	1	11	60.7	
II	Controls	50	4	6	9	1	30	34.8	Quinidine administered after operation
	Treated§	47	4	8	4	1	30	30.3	
III	Controls	25	0	0	0	1	24	4.0	Received quinidine then etherized; no operation
Total . . .		182	13	30	24	4	111		

* Under this heading are listed deaths due to the anesthetic and to hemorrhage from the heart.
† This includes deaths not due to hemorrhage and occurring within the first postoperative day.
‡ In calculating mortality the operative deaths were omitted from consideration.
¶ These animals each received quinidine, 0.01 gm. intraperitoneally, immediately prior to the operation, followed by 0.02 gm. daily orally, thereafter.
§ These animals received quinidine in similar dosage except that the intraperitoneal dose was given immediately after the operation.

The *complete date of mortality* are shown in Table 1. One can note here a definite discrepancy between the experiments in which quinidine was given preoperatively and those in which it was administered after the operation. It is clear that the administration of the drug prior to opening the chest resulted in a definitely higher mortality than was observed in the controls. It can be noted that this increase in mortality occurred almost entirely in the immediate postoperative period. (The term "postoperative" is here used to include all deaths from the time the chest wall was closed until the next morning.) Most of

the deaths so listed occurred immediately after closing the chest and were due to failure of the animals to breathe. In a few instances respiration began and then ceased within the next hour or two. The difference between the controls and the treated animals in regard to postoperative mortality was so striking that it could hardly have been due to chance. On the other hand, the mortality was somewhat greater during the subsequent period in the controls than in the animals receiving the quinidine. At the end of 3 weeks the total mortality was 40.7% of the controls and 60.7% in the animals receiving the quinidine, the difference being due to the greater incidence of the immediate postoperative deaths in the latter group.

When, on the other hand, the quinidine was administered postoperatively, *i. e.*, after the animal had recovered from the respiratory failure induced by the ether and the thoracotomy, the results were different. Here the mortality was slightly less in the animals receiving quinidine, but the difference between the two groups was so slight as to be of questionable significance.

In order to determine whether the doses of quinidine were in themselves toxic, additional control observations were made. Twenty-five rats were given intraperitoneal quinidine comparable to that received by the experimental animals, and were then subjected to ether anesthesia without an operation being done on the chest. Of these 25 animals, all survived the immediate procedure, and only 1 died in the following 3 weeks, this animal dying of intercurrent disease. It may therefore be concluded that quinidine in the amounts employed is not seriously toxic for normal rats.

At the beginning of the experiments, we had expected that if quinidine had any protective value this would be most pronounced if the drug were given preoperatively. However, the results mentioned indicated that this assumption was quite erroneous. The drug appeared to be harmful on preoperative administration and was either ineffective or slightly beneficial when given postoperatively. Observation of the animals indicated, as mentioned, that the increased mortality in those rats receiving quinidine preoperatively was due mainly to difficulty in establishing respiration immediately after closing the chest. Since inspection of the tongue indicated serious anoxia in practically every animal, it was thought that the increased mortality in the animals receiving quinidine preoperatively might have been related in some way to the combined effect of anoxia and quinidine. Accordingly, a series of experiments was done to test this point.

Animals were placed in glass jars and subjected to reduced barometric pressure (see Table 2). Of 13 control rats not receiving quinidine, 5 died from the effects of anoxia. Of 13 rats receiving quinidine, 3 died from exposure to a comparable degree of anoxia. The series is too small to justify the conclusion that quinidine tended to protect the animals from the effect of anoxia, but it does indicate that the drug did not make the animals more susceptible to death from anoxia. Another point of interest is illustrated by these experiments. It was found, as would be expected, that animals subjected to myocardial

injury a short time before, were decidedly more susceptible to the effects of anoxia than were normal animals.

TABLE 2.—EFFECT OF QUINIDINE ON SENSITIVITY OF RATS TO ANOXIA

Condition of rats	Duration of exposure to anoxia (min.)	Barometric pressure (mm. Hg)	Control rats		Rats receiving quinidine*	
			No. of animals	Deaths	No. of animals	Deaths
Normal	38	320	1	0	1	0
Normal	58	280	2	0	2	0
Normal	22	200	2	1	2	0
Heart seared 7 days before	39	200	2	1	2	1
Heart seared 30 min. before	30	280	6	3	6	2
Total	..	..	13	5	13	3

* These animals received quinidine sulfate, 0.01 gm. intraperitoneally, immediately before exposure to reduced barometric pressure.

Since the experiments indicated that oxygen deficiency could not be held accountable for the increased mortality in the series of animals receiving quinidine preoperatively, it was thought that the anesthesia might in some way be responsible. Induction of anesthesia by ether, the anesthesia being severe enough to allow one to operate on the chest, did not result in a significant mortality, for, as mentioned, 24 of 25 such animals which also received quinidine survived, a single death being due to intercurrent disease. However, in these experiments the degree of anesthesia did not proceed to respiratory failure, while in the animals subjected to myocardial searing, respiratory failure occurred in a large percentage; because in addition to the ether anesthesia, these animals had their chests opened for a period of ½ to 2 minutes. Consequently, it was thought that a deeper degree of ether anesthesia, proceeding to the point of respiratory paralysis, might throw some light on the toxic effect of quinidine. Accordingly, the following experiments were done:

TABLE 3.—EFFECT OF QUINIDINE ON RECOVERY FROM RESPIRATORY PARALYSIS INDUCED BY ETHER

Duration of apnea,* (sec.)	Controls		Quinidine	
	No. of animals	Deaths	No. of animals	Deaths
15	1	0	1	0
20	3	0	3	1
25	4	1	5	1
30	5	2	4	1
35	2	1	2	0
40	18	3	18	12
Total	33	6	33	15

* This denotes the interval between cessation of breathing—induced by ether—and the institution of artificial respiration.

Sixty-six rats were placed in ether jars and kept there for varying periods following the onset of apnea. Half of these animals had been given quinidine—0.02 gm. per rat, intraperitoneally—prior to the induction of anesthesia. The experiments were quite convincing.

Of the 33 control animals, only 6 succumbed, while of the 33 animals receiving quinidine prior to the induction of respiratory failure by ether, 15 succumbed (Table 3). It therefore seems clear that the increase in mortality in the animals which were treated with quinidine prior to the operation on the heart, can be ascribed to the effects of this drug, in tending to cause fatal respiratory paralysis. This conclusion is in keeping with the observations of Gordon, Matton and Levine,[3] who observed in cats that death due to quinidine usually occurred as the result of paralysis of respiration.

The other point of interest in the studies is the possible significance of the fact that in the series of animals receiving quinidine postoperatively, the mortality was somewhat lower than in the controls. The difference in total mortality was slight, but if the first postoperative day was omitted from consideration the animals receiving the drug exhibited a decidedly lower mortality (Table 1).

Discussion. The data which have been presented seem to justify the following conclusions: (1) Under the conditions of these experiments, the administration of quinidine subsequent to the production of myocardial injury caused a slight decrease in mortality. (2) The administration of quinidine prior to the production of myocardial injury caused a significant increase in mortality, such increase being due to the effect of the drug on depressing the ability of the animal to recover from respiratory failure.

Caution is naturally necessary in attempting to apply the results of a study on animals to the problem of the use of quinidine in patients with coronary thrombosis. In the first place there is the species difference; in the second place the type of injury produced by burning the myocardium is not strictly comparable to that induced by occlusion of one of the coronary vessels. Consequently, in the following discussion, the opinions expressed are based not only on these experiments but on our own clinical observations, as well as on experience of others as available in the literature.

There appear to be certain definite *contraindications to quinidine.* Among these is the presence of heart failure. Thus, the recent study of Smith and Boland[9] indicated that sudden death following quinidine administration is likely to occur when the drug is administered to patients with congestive failure and is very rare in the absence of this condition. These authors believed cardiac standstill to have been responsible for the instances of sudden death occurring in their series of patients. However, the observations on cats of Gordon, Matton and Levine,[3] as well as those reported on rats in this communication, indicate another possible explanation. These studies show that doses of quinidine which are ordinarily harmless may favor the development of respiratory paralysis, provided the breathing is already seriously disturbed. Hence, it appears possible that a similar mechanism may operate to produce death from respiratory failure when the drug is administered to patients already having disordered breathing as the result of cardiac failure.

In regard to the possible dangers of quinidine administration, one

has to distinguish heart failure of long duration dependent on chronic myocardial disease and without a complicating arrhythmia, from heart failure of short duration dependent on acute myocardial injury and precipitated by an arrhythmia. Thus, a person progressing favorably after coronary thrombosis may develop congestive failure following the onset of ventricular tachycardia, and in such conditions the administration of quinidine may be life-saving because the drug may abolish the ectopic rhythm. Similarly, we have seen several patients who developed auricular fibrillation for the first time shortly after coronary thrombosis and who as a result of the tachycardia and the arrhythmia developed congestive failure. In such patients likewise the drug should be used. On the other hand, when the heart failure has not been precipitated by the arrhythmia and when it is of longer duration, it would seem that the administration of quinidine is dangerous.

Although our experiments did not seem to indicate any particularly greater incidence of bradycardia and block following the administration of quinidine, there is neverth less ample evidence in the literature to demonstrate that the drug may aggravate a preëxisting auriculoventricular or intraventricular block. (There is very little evidence that the drug will produce block in persons who have no disturbance of conduction and, in fact, our results, having been obtained on the hearts of normal rats, support this conclusion.) It would seem that quinidine is contraindicated in patients who have either auriculoventricular or intraventricular block, or who have a condition which is likely to lead to such disturbances of conduction. Since these complications develop much more commonly in persons with posterior than in those with anterior infarction, one should be especially cautious in administering quinidine to patients with posterior lesions. In order to make the distinction with certainty it is necessary to take electrocardiograms, and as a rule it would seem unwise to give quinidine to a patient without a previous electrocardiogram.

Aside from the presence of congestive failure and of auriculoventricular or intraventricular block, there are certain other conditions which probably constitute contraindications for quinidine. One of these is long-standing auricular fibrillation. Although embolism following the reëstablishment of regular rhythm is probably much less frequent than has formerly been supposed—it did not occur in any of the 41 cases reported by Smith and Boland[9]—this complication nevertheless has been reported in the literature and we have seen one instance which was probably the result of quinidine administration. Furthermore, there are certain patients with auricular fibrillation in whom the drug increases the heart rate by causing a change in the mechanism to that of flutter. Such an occurrence is exceptional and should not mitigate against the use of quinidine when auricular fibrillation suddenly develops as a complication of coronary thrombosis, and when there are no other contraindications to its use.

When we turn from the contraindications to a consideration of the *indications for quinidine* in persons with acute myocardial injury the

situation is somewhat less confused. In ventricular tachycardia, which is not a rare complication of myocardial infarction, the drug may be of great value. In auricular fibrillation of recent onset, quinidine would seem to be reasonably safe, provided none of the contraindications which have been cited exist. The most common indication for quinidine in patients with coronary thrombosis would seem to be anterior infarction with frequent premature beats. There is evidence to support the assumption that patients with frequent ventricular premature beats are more likely to develop ventricular fibrillation than individuals in whom this arrhythmia is absent. We have repeatedly administered the drug under these conditions and have usually observed a prompt cessation of the extrasystoles. No untoward effects have been observed in any patient. The question as to whether quinidine should be given to individuals with posterior infarction and premature beats is a more difficult one and will probably not be answered by any generalization. If the extrasystoles are quite numerous and the patient presents no evidence of conduction defects, quinidine should probably be given. If, on the other hand, there are only occasional premature beats and definite evidence of auriculo-ventriculo-intraventricular conduction defects exist, the drug would seem to be contraindicated.

Auricular flutter is a rare complication of coronary thrombosis, but occasionally occurs. We have seen one patient in whom the rate could not be slowed by digitalis but quinidine caused a prompt reversal to the normal mechanism with slowing in rate. Auricular premature beats, of sufficient frequency as to be important, and paroxysmal auricular tachycardia are rare complications of coronary thrombosis. Neither of these arrhythmias respond particularly well to quinidine. On the other hand, nodal tachycardia occasionally occurs, and we have seen several instances in which this arrhythmia had been refractory to other means of treatment and has yielded promptly to adequate doses of quinidine.

Another problem which has been discussed by several authors is whether quinidine should be administered routinely to all patients with coronary thrombosis who present none of the contraindications. The purpose here, of course, is to try to prevent ventricular fibrillation and sudden death. On the basis of the available evidence, our own belief is that this should not be done because some of the patients with posterior infarction may later develop conduction defects as the result of the infarct, and such defects would increase the likelihood of catastrophes from quinidine. There still remains the problem as to whether one should give the drug routinely in patients with anterior infarction irrespective of the presence of any arrhythmia and in the absence of any contraindication. Our results on the rats with experimental myocardial injury, as well as the observations of Smith, McEachern and Hall,[8] might be interpreted to support such a usage of quinidine. On the other hand, the difference in mortality in the treated and untreated animals was not great in our series, and the likelihood of toxic effects of quinidine would seem to be less in the previously

normal hearts of the animals than in the abnormal hearts of patients with coronary disease. Therefore, until further evidence is available it would perhaps seem wisest not to give the drug routinely to patients with anterior infarction, but to reserve its use for individuals with the arrhythmias which have been discussed and, except in the case of ventricular tachycardia, to withhold it when the contraindications which have been mentioned are present. Our data would suggest that the dangers from the use of the drug are greater during the first 24 hours after myocardial injury than at a later date when the protective action is apparently greatest.

Operations on the heart are becoming more common and will probably increase in frequency during the war. It has been suggested by Beck and Mautz[1] that the routine use of quinidine in patients subjected to operations on the heart might decrease the incidence of sudden death. Our experiments would suggest that, if the drug is to be used in such patients, it should be withheld whenever there is any well-marked dyspnea or when any respiratory disturbance is likely to develop as the result of the anesthetic or the operative procedure, because it seems that the existence of a disorder of breathing markedly increases the likelihood of respiratory failure and sudden death following the administration of quinidine. A similar procedure would seem to be wise in the case of patients subjected to thyroidectomy. Here quinidine has been sometimes used in order to try to prevent postoperative ventricular fibrillation. We have used it preoperatively in a number of such patients and have never seen any untoward results. However, in view of the increased mortality in our animals when quinidine was administered preoperatively, we believe that in thyrotoxic patients the drug, if employed, should be used after the operative procedure has been completed.

Summary and Conclusion. The effect of quinidine was studied on the mortality of rats subjected to experimental myocardial injury. The following results have been obtained: (1) When the drug is administered preoperatively, there is a definite increase in mortality. This increase has been shown to be related to the depressing effects of the drug on respiration. (2) When the drug was administered postoperatively, there was a slight decrease in mortality and an apparently significant decrease in deaths occurring after the first 24 hours. (3) The indications and contraindications for quinidine in patients with myocardial infarction and in persons subjected to operative procedures on the heart have been discussed. It is concluded that the available evidence does not favor the use of the drug routinely for such patients, and that if it is to be employed its administration should be begun after several days have elapsed following the onset of symptoms.

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PROGRESS
OF
MEDICAL SCIENCE

PEDIATRICS

UNDER THE CHARGE OF
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URINE ANALYSIS IN PEDIATRICS; TEN YEARS PROGRESS

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The purpose of this Review is to survey those advances in urinalysis of the past decade which are of importance in the medical management of pediatric patients. Designed to be practical rather than academic, the survey has been deliberately limited to tests of substances within the scope of the average technician with the equipment found in most clinical laboratories. More difficult technical problems which need handling by specialized skills and apparatus, such as hormone measurements, vitamin assays and creatine and mineral balances, are ignored or given but passing mention. Omitted also are descriptions of the intriguing liver and kidney function tests—the hippuric acid excretion test, the inulin and diodrast clearances, the hexose tolerance tests, the pituitary concentration test, and the like. For completeness sake it has been necessary with some topics to refer to occasional scientific contributions made prior to 10 years ago.

The subjects discussed comprise: (1) proteinuria; (2) quantitative counts of urinary sediments; (3) melituria; (4) sulfonamides; (5) pigments; (6) findings in newborn and premature infants, and (7) other miscellaneous items.

1. **Proteinuria.** Traces of mucinous proteins can be demonstrated in all urines,[112,155] if carefully looked for by refined techniques. This holds for both children and adults. For 5 normal boys 2 to 7 years of age having urines negative with 20% trichloracetic acid, Wang and Wu[155] found a daily elimination 5 to 14.2 mg. The exact quantities varied from day to day and from child to child. Proteins of this sort escape detection in the routine precipitation tests, which are less highly sensitive and pick up only serum proteins when present.

Proteinuria Associated With Physical Activity. That violent exercise or physical activity will induce proteinuria is almost too well known to require comment, but 2 recent studies on subjects in the pediatric age group have been reported. Thirty-seven boys 7 to 13 years of age, were tested, after racing, by Nakagawa and Kawamo.[114] Following short footraces (40, 60, or 135 meters) proteinuria appeared in 2 boys; following a long race (1200 meters) proteinuria appeared in 35 of the 37. Parenthetically, glycosuria never was noted. Of 36 high school athletes, aged 16 to 18 years, tested after football practice, Preston[123] found protein, casts, red cells and leukocytes in the urine of 6. Preston followed the urines of

15 of these players through the football season, and found only 3 that never exhibited proteinuria after at least 1 game. The encountered concentrations of protein in the urine ranged from 0.5 to 6 gm. per 100 ml. After the playing season was over, the urines of all but 1 youth again became protein-free.

Febrile Proteinuria. Of 11 different diseases in 300 patients studied by Ehrström,[51] pneumonia and influenza gave rise to proteinuria 10 times as often as did any of the others. Neither duration nor height of the fever appeared to be of influence. Ehrström concluded that the pneumococcus must play a somewhat specific rôle in causing kidney damage.

Intermittent Proteinuria. References to the many early studies on the frequency of so-called intermittent or postural or *orthostatic* proteinuria in childhood can be found in the paper by Calvin, Isaacs and Meyer[30] in 1926. Studies since that time on large groups of children have apparently not been reported.

The literature concerning the etiology of orthostatic proteinuria was recently reviewed by Young, Haines and Prince.[163] The chief theories as to its etiology were later listed by Prince:[124] (1) Increased lordosis of the lumbar spine causing mechanical obstruction to the renal circulation. (2) Decreased renal blood flow concomitant with the fall in pulse pressure in the upright position. (3) Vasomotor instability. (4) Subnormal constitutional development. (5) Reflection of a general lowered condition—asthenia, malnutrition, lowered vitality and resistance. (6) Imbalance of the autonomic nervous system. (7) Actual lesion of the renal substance, very mild in character, not demonstrable by ordinary methods. (8) Focal infection in some cases. Other names which have been used to describe the condition are benign, functional, growth, adolescent, physiologic, intermittent and cyclic proteinuria.

Intermittent proteinuria is no longer interpreted as a sign of disease of the kidney. This conclusion is based upon accumulated clinical experience which can be summarized under 4 headings:

1. In otherwise normal individuals, intermittent proteinuria has a high rate of occurrence as compared with the relative infrequency of the nephritic disorders. On testing the urines of 50,000 British soldiers during World War I, MacLean,[97] after deductions for pus or spermatozoa and of those with "less than 5 mg. per 100 cc.," demonstrated an incidence of 2.2%. McLeod and Ameuille,[107] in 1916, encountered 263 positive (3.7%), in 7041 French and British troops. Of 2269 West Point cadets and officers, Ashburn[10] found 360 (16%), with proteinuria. In 20,000 men entering the University of Minnesota, Diehl and McKinlay[42] found an incidence of 1065 (5.32%). On reëxamination, approximately 75% of those who had had a trace on entrance were protein-free. Bashford[14] examined, 25 years later, some 30 men who had shown proteinuria when 14 to 16 years of age, and found only 1 still with protein in the urine. Of 3642 students entering the University of Pennsylvania, Burden[27] found 949 (26%), positive 69.3% of these were negative on reëxamination. Blatherwick[21] reported on the urine findings in 15,000 employees of the Metropolitan Life Insurance Company, a group representative of the general population in age and sex distribution and state of health; 91.6% were negative, 3.3% had about 10 mg. of protein per 100 ml. and 1.7% had 20 mg. or higher. Of 4500 male youths aged 14 to 17, examined in Vienna during 1932 and 1933 by Nowak,[116] 624 (11.1%), had orthostatic proteinuria, whereas but 36 (0.8%), had chronic kidney disease. Calvin, Isaacs and Meyer,[30] found the incidence to be 60% in 189 poor children and only 5% in 331

children from a well regulated orphanage. They ascribed the higher rate to the poor hygienic surroundings, the poorer state of nutrition, and the many untreated foci of infection.

In Wolman's[162] study of the admission urine specimens of 22,000 presumably healthy American men entering the U. S. Maritime Service, of 400 completely studied instances of proteinuria, 382 were found to be intermittent or "orthostatic," and only 8 were proven to be nephritic. In another series of 110 men with urines negative on arrival, 56% showed proteinuria at least once when tested 8 times in a 5-day period. This latter study demonstrates that the values reported for the frequency of proteinuria must be viewed as minimal when based upon single specimen determinations, since random specimens will often fail to uncover the disturbance.

2. Intermittent proteinuria displays a definite cycle in relation to age. Its incidence rises from the sporadic childhood level to reach a maximum during the years of puberty and adolescence, and then declines rapidly above age 18 to become negligible above age 25. Thus, in Lauener's[86] investigation on 5000 school children, there was found an incidence of 6.7% in 1246 children aged 6 to 7 years; of 27% in 1350 children 10 to 11 years; and of 38% in 2481 adolescents 15 to 16 years of age. The percentages at all ages were higher for girls than for boys. It should be pointed out the protein shown by most of the children was in trace amounts. Lee[87] noted, among Harvard freshmen of average age 18, that proteinuria occurred in about 5%; whereas, in upper classmen of average age 20, the incidence was 3.5%. Diehl and McKinlay's[42] college freshmen were 5.32% positive; whereas MacLean's[97] soldiers, older in age, were but 2.2% positive. In Thorp and Wakefield's[152] 100 Mayo Clinic patients with age range 4 to 47 years, 26 were 12 years old or less, 67 were between 12 and 30, and only 7 were 30 or over. In 64 cases collected by Young, Haines and Prince[163] from the Johns Hopkins Hospital files, the ages ranged from 9 to 39 years, the majority being between 14 and 18 years. In Wolman's[162] series, the incidence among Maritime Service trainees was highest at age 16 and declined quickly in men but a few years older.

3. There are two principal differences in the urine findings between intermittent proteinuria and true nephritis: (*a*) In nephritis the excretion of protein is continuous rather than inconstant, regardless of posture or exercise.[53,63] Occasional instances of mild chronic glomerulonephritis which are subclinical for years, and the nearly well patients convalescing from acute nephritis, seem to be the only exceptions to this rule. With such cases the proteinuria may usually be elicited by active work or lordotic posture,[53] though absent or slight when resting. Sometimes, too, a mild nephritic proteinuria can be made to clear transiently by the forcing of fluids or administration of alkali in large doses,[63,108,121] though generally speaking proteinuria persists constantly in active nephritis. (*b*) In addition, erythrocytes and casts appear regularly in the sediment during nephritis. Even the above-mentioned exceptional mild or latent cases with inconstant proteinuria usually excrete an increased number of red cells or casts, to be detected by careful microscopy or quantitative procedures such as the Addis sediment count.[3,4] Intermittent proteinuria usually gives rise to no abnormal microscopic findings.

4. Actual follow-up studies of individual cases have brought out the harmless and benign character of intermittent proteinuria. Thus, when Palmer[118] tracked down, after 8 or more years, 35 former college students who had once had proteinuria, only 2 still exhibited traces in the urine.

Of 35 others who replied to a questionnaire, not one was having symptoms of renal disease. After an average interval of 7 years, 64 cases were re-examined by Thorp and Wakefield,[152] and all but 1 were in good health. Of 18 others that had had persistent proteinuria with an orthostatic increase, only 2 showed renal disease an average of 7.7 years later; the urine of the other 16 had become entirely negative. Nor did any of Lee's[87] students with proteinuria develop nephritis over a 5-year observation period. Of 14 patients followed by Young *et al.*,[163] 4 were protein-free in 2 years, 6 in 3 years, 1 in 6 years, and 3 in 12 years. Evers[55] reported that, after 9 years, insurees of the New York Life Insurance Company who had had proteinuria without casts or other evidences of nephritis, showed no increase in mortality above normal expected levels. Similarly, Christiernin, Dublin and Marks,[34] in a survey of policies issued by the Metropolitan Life Insurance Company from 1925 to 1935, and studied in 1937 and 1938, found no unusual mortality in otherwise normal proteinuric individuals, though when the proteinuria had been associated with hypertension or obesity the mortality was much above normal expectation. MacLean[97] found the distribution of "trench nephritis" no higher among troops who had had a positive protein test earlier in the campaign than among those whose urine had been negative. Of the 22,000 men studied by Wolman,[162] 27 cases of acute glomerulonephritis and 7 cases of acute pyuria developed subsequent to entry for training, but not one single instance came from the group of 400 individuals with proteinuria in the initial arrival specimens.

Thus, from the evidence tabulated above, it may be concluded that when careful study uncovers no signs of nephritis or other renal disease, particularly when the subject is young, simple proteinuria of the intermittent type should be interpreted as a temporary reversible dysfunction and not as a positive or potential state of disease.

Concentration of Protein. With kidney disease, as is well known, the excretion of protein may range from 5 gm. per 100 ml. of urine or higher. In nephrosis or severe nephritis down to the faintest detectable trace, 5 mg. per 100 ml., or even none at all in convalescent nephritic patients when recumbent. Similarily in benign intermittent proteinuria the range may be nearly as great, from faint traces to at least as high as 3 gm. per 100 ml.[162] In urologic lesions, proteinuria is irregular and unreliable as a diagnostic sign. It is evident, therefore, that the magnitude of the concentration of protein in individual specimens of urine is of little aid as a definitive criterion for distinguishing among the various types of proteinuria. Viewed statistically, however, the *mean* values for the concentration of protein are of greater magnitude in patients ill with kidney disease than in subjects having benign proteinuria.[162]

In this connection, one may mention the observations on adults with chronic nephritis by Berglund, Scriver and Medes.[18] These workers found a temporary increase in protein elimination on the change from resting to active walking, and a more permanent rise after the change from a low to a high protein intake. They found, too, that the *rate* of protein excretion per hour remained about the same regardless of whether there was diuresis or a scanty highly concentrated urine. Hence, one cannot estimate the total daily excretion of protein from the amount in a single urine sample, without taking into account specific gravity and rate of diuresis. In acute nephritis, Berglund and Frisk[17] noted that the rate of proteinuria is subject to quick inexplicable changes, irrespective of diet, particularly in the direction of improvement.

In intermittent proteinuria, as the name indicates, no constancy prevails. Urine specimens may be entirely protein-free at any time during the day as well as in recumbent inactivity. With many subjects, the assuming of a lordotic posture for an interval of time will not aggravate the protein elimination, though the majority do respond in this way.

Nephritis. ¹ *Pathogenesis of Proteinuria.* Though traditionally referred to as "albumin," urinary protein ordinarily consists of both albumin and globulin. The literature dealing with the nature and origin of the urinary proteins in renal disease was reviewed in 1936 by Bing,[20] to whose article the reader is referred for specific references. He pointed out that blood and urine proteins have been proved identical in chemical composition, in physical properties such as optical rotation, racemization, osmotic pressure and specific refraction, and in immunologic responses to precipitation, complement fixation and hemolysis reactions; on the other hand, proteins extracted from the kidney exhibit no such corresponding identity. Additional evidence that the urine proteins come from the blood is the lowering of the level of plasma protein in patients with proteinuria; it would seem impossible for the renal parenchyma to secrete such large quantities of protein as are excreted daily in severe proteinuria.

Moreover, the urine proteins are not abnormal plasma proteins removed as foreign bodies or as elements in a detoxication process. Bing emphasized that the diffusibility of the serum proteins is no greater in the proteinuria patient than in normal individuals. Intravenous injection into healthy animals or men, of either serum or urine protein from patients ill with nephritis, will not cause proteinuria. On transplantation of a healthy dog kidney to the neck of a dog having uranium nephritis, no protein will be excreted through this "neck-kidney," whereas similar transplantation of a uranium nephritis kidney to either normal or nephritic animals will be followed by proteinuria from this kidney.

The leakage of protein is greater in nephrosis and amyloidosis than in glomerulonephritis and nephrosclerosis. With all of these conditions, Bing found fairly constant values for protein excretion from day to day under constant conditions, though the quantity rose and fell parallel with the protein content of the diet, and there was a rise after acid ingestion and in fever. These variations were appreciable and not related to corresponding variations in the creatinine clearance. The more prominent the glomerular lesions, the greater the excretion of large moleculed globulins. With cases having badly damaged glomeruli, as in beginning glomerulonephritis or late chronic glomerulonephritis with renal insufficiency, the ratio of albumin to globulin in the urine is low—between 3 and 10; conversely, in nephrosis, which has slight anatomic changes, the ratio becomes high, there being 10 to 20 times as much albumin as globulin. The very large molecule of fibrin is encountered but seldom in the urine. The foregoing statements from Bing's paper epitomize the current concepts of the genesis of the urine protein in nephritis. In the present Review the literature on the metabolic disturbances occurring in nephritis will not be touched upon.

The quantity of protein reaching the urine may not be dependent solely upon glomerular leakage, according to Addis,[3c] who was interested in Walker and Oliver's[154] observation that an animal's glomerulus may leak protein up to 30 mg. per 100 cc. of glomerular filtrate. If a human subject lost but 20 mg. per 100 cc. in his usual 24-hour glomerular filtrate of 180,000 cc., the total excretion per 24 hours would amount to 36 gm. of protein. Inasmuch as actual excretions during proteinuria are much

lower than this amount, and in the light of suggestive experiments of Gérard[67] and Randerath,[126] Addis suggested that some tubular resorption of protein may take place in the human kidney.

In boys before puberty, proteins from the prostate or seminal vesicles will not appear in the urine after local massage of the parts, according to Calvin,[28] and therefore the proteinuria found in subjects of this age cannot be attributed to such substances.

2. **Sediment Counts (Addis).** A small number of formed cellular elements can usually be recovered from any specimen of normal urine if intensive search is made. It is the increase in the quantities of these elements which assumes importance as one of the cardinal attributes of the disease, nephritis. For quantitative enumeration of cells and casts, the method proposed by Addis[3a,b] is in widest use. This technique counts all the red cells, leukocytes and casts which are passed in a 12-hour period. For best results, the patient should have a low fluid intake for half a day prior as well as during the test period and not be receiving alkali medication, in order that the urine when passed for collection be acid and not dilute. These precautions, plus a few drops of strong formalin placed in the collecting vessel, are essential to preserve the cellular elements from lysis, yet most laboratory manuals fail to so advise. Many published studies on results and interpretations of the test omit specific mention as to whether such measures had been taken in the gathering of their data. Since the sources of error are many, it is wise to do counts in duplicate.

Wide variations occur in normal subjects, and no close division can be drawn between normal and abnormal. As Addis[3a] pointed out, the method is not strictly quantitative; its chief intent is to express the rates of excretion in terms of approximate magnitude. Fluctuations in specific gravity and urine volume are more likely to occur in childhood than in adults, according to Lyttle,[96] who recounted the difficulties in making children coöperate in the restriction of fluid intake for the necessary 24-hour period.

Normals. Most of the reports on record deal with adults. However, a few pediatric workers[24,28,96,129,131] have commented most favorably on the usefulness of the Addis count for following the progress of recovery from acute nephritis. Before reviewing their findings, it is essential to have normal values clearly in mind. The upper limits of excretion for a 12-hour period in healthy children under 13 years of age, as compared with adults and expressed in round numbers, stated as follows:

Author	*No. of children*	*Casts*	*Erythrocytes*	*Epithelial cells and leukocytes*
Addis[3] (for adults)	..	5,000	500,000	1,000,000
Rew and Butler[129]	16	38,000	275,000	850,000 (boys) 4,000,000 (girls)
Lyttle[96]	74	10,000	600,000	600,000 (boys) 1,000,000 (girls)
Soto[143]	306	7,300	950,000	3,000,000
Boyle *et al.*[24] (postnephritic children)	25	18,600	115,000	1,000,000

In nephritis the shedding of cellular elements into the urine becomes greatly increased, the magnitude of the sediment counts being from 2 to higher than 1000 above these upper normal limits.

Nephritis. Snoke[141] listed several "compelling reasons" why the Addis concentration method is essential for intelligent diagnosis and prognosis in

cases of renal disease: (*a*) Preservation of the formed elements is satisfactory only by this method. Snoke cited instances with low specific gravity or alkaline reaction and no casts or R.B.C. in the routine specimens; yet the patients were ill with active nephritis and large numbers of casts and R.B.C. could be demonstrated by the concentration technique. (*b*) Exact measurement of the numbers of cells and casts excreted is more dependable than estimates made by ordinary techniques. Thus, one or two R.B.C. per high-power field seen in an ordinary test, may be regarded as having little significance, yet if the specimen is dilute this number may be representative of an excretion of several million cells per 12 hours—a significant figure. (*c*) No other method affords reliable comparison of the specimens with each other and the determination with reasonable accuracy of increase and decrease of formed elements. Fluctuations in dilution and hydrogen-ion concentration make the ordinary tests nearly worthless for quantitative recognition of changes for better or worse in renal lesions. (*d*) The Addis count is a more delicate test for renal disease than is the blood urea level, phenolsulfonephthalein excretion and other functional tests which often give normal values in the presence of mild or minimal nephritis. For example, Snoke was able to uncover 14 mild chronic cases of glomerulonephritis in one children's clinic by following up with the Addis test healthy appearing youngsters who had exhibited mild albuminuria, hematuria or casts in their preoperative routine urinalyses.

Rubin, Rapoport and Waltz[131] found the red cells to be the most constant and persistent abnormality of the Addis count. Taking the value of 1,000,000 red cells per 12 hours as the upper limit of normality, these workers found that during recovery from acute glomerulonephritis there is a correlation between the return of the sedimentation rate and the red cell count, though the latter usually becomes normal about 5 weeks later than the sedimentation rate. In 40 children with acute glomerulonephritis, the routine urinalysis returned to normal on the 37th day, on an average, whereas the Addis count required 120 days to achieve normality. There was a close correlation between the number of days it took for the 12-hour R.B.C. excretion to drop to the 10 million level (70 days) and the time required for the sedimentation rate to become normal (86 days). In an 8-year experience they saw no recurrence of acute glomerulonephritis in any patient who had shown a complete recovery (by Addis count and sedimentation rate) following the first attack.

Other Diseases. In children with acute infections, Rew and Butler[129] found, by means of Addis counts, that the urine sedimentary elements tended to be more abundant than in control children free from infections.

Lyttle[96] performed sediment counts 3 times weekly on 14 cases of scarlet fever. His patients were males aged 4 to 14 years, kept in bed on a low protein-low salt diet. One had had scarlet fever 7 years previously, and another had had acute glomerular nephritis following tonsillitis (hemolytic streptococcus) a year earlier. None of the 14 patients developed clinical signs or symptoms of postscarlatinal nephritis, but every one showed a moderate transient increase in the excretion of protein and formed elements at some time between 8 to 45 days after onset of the scarlet fever. The highest levels reached (per 12 hours) were: for protein, 174 mg.; for casts, 1,320,000; for R.B.C., 12,915,000; for epithelial and W.B.C., 9,460,000. Lyttle's comment was that it is difficult to draw any definite line between these subclinical signs of renal irritation and true postscarlatinal nephritis, though red cell excretion in an ordinary hospital case

of nephritis is usually in the hundreds of millions. On reviewing the medical literature, he found a number of other reports which, while not quantitative, showed that the great frequency of renal irritation in scarlet fever was already well known. Lyttle's studies confirm this indisputably, and emphasize that microscopic hematuria can be detected much more dependably by the Addis method than by routine urinalysis.

Orthotolidine. Orthotolidine (*not* orthotoluidine) is more sensitive and more dependable than guaiac or benzidine for the detection of blood in urine. This reagent, first utilized for detection of blood by Ruttan and Hardisty[132] in 1912, was recommended for the detection of occult hematuria by Stone and Burke[145] in 1934. Barach and Pennock[12] found orthotolidine useful for this purpose. Its application to the pediatric problem of nephritis was explored and found satisfactory by Calvin and Carbone[29] and Weiner and Schwartz.[157] The test is simple to perform. To the centrifuged sediment of 15 ml. of urine resuspended in 1 ml. of urine are added 2 drops of 1% orthotolidine solution in pure methyl alcohol, and 2 drops of a mixture of glacial acetic acid 1 part and commercial hydrogen peroxide 2 parts. A transient blue color represents a positive result, the intensity of the color paralleling roughly the number of red cells present. Weiner and Schwartz compared the findings of the orthotolidine test with those of the Addis count in children recovering from acute nephritis. They secured positive results with the chemical test when the Addis red cell count was 17,250,000 or higher; they concluded that this test was not delicate enough to pick up low orders of pathologic excretion of red cells. In the Reviewer's experience, however, the threshold for positive reaction with orthotolidine is lower and more sensitive than the above value.

3. **Melituria.** The sugar most frequently found in children's urine is dextrose or glucose, but pentose, fructose, galactose, sucrose and more complex polysaccharides may be found at times. Most American workers restrict the term *glycosuria* specifically to dextrose, and apply *melituria* more broadly to designate abnormal excretion of any sugar in the urine. Melituria, as observed in adults, has been well surveyed in recent years by Bock,[22] Cantarow and Trumper,[32] Marble,[100] Reiner,[127] and others. The discussion which follows emphasizes those aspects which are of importance to the pediatrician, many of which have been ignored in the reviews planned for the internist.

It is an axiom of good pediatrics that any infant or child having persistent sugar in the urine be given a diagnostic study. Granting that diabetes in childhood is rare in comparison with the relatively great frequency of melituric reactions, there is always the possibility that the subject in question has the disease. Even when the condition turns out to be a benign glycosuria of alimentary, emotional or low renal threshold origin, or one of the less familiar melituria, the information now secured will be of service in future years if the excretion of sugar persists or recurs.

Techniques for Recognition and Identification. It is important first of all to make sure that the performance of the urinalysis itself is free from technical error, since the tests for sugar are often not properly made. For the initial recognition of sugar, the widely used Benedict's qualitative copper reagent is superior to both Trommer's and Fehling's reagents, in that it gives fewer false positive reactions. It must be remembered that saccharose or sucrose is not revealed with these reduction methods. In urines containing 0.03 to 0.15% creatinin, which is the range occurring in the majority of human urines, the Benedict test has a threshold sensi-

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tivity of about 0.05%, or 50 mg. of sugar per 100 ml. of urine.[135] The minute quantities of dextrose and other reducing substances which escape normally into all urine specimens are of a lesser order of magnitude and will not be caught by this test. The roster of these other reducing substances comprises, among others, ascorbic acid, the glucuronic acids, uric acid, creatinin, di- and polysaccharides derived from dextrinous foods, and derivatives of salicylates or cinchophen when these are being taken by mouth. Reference to Benedict's[16] original paper shows that the boiling time originally recommended for the test was but 1 to 2 minutes. Folin and McEllroy[65] have indicated that 3 minutes in a boiling water bath is equivalent to 2 minutes over a flame. The presence of excess reducing sugar will become manifest by that time.[135] For extreme accuracy, the reading should be made at once when the specimen is taken from the source of heat, and not after it has been kept standing hot for some moments longer. The 5-minute period instructed by most texts is too long, since reducing substances more slowly acting than the hexoses may then evoke false positive readings. When the qualitative test is positive, it should be followed by a quantitative reduction test to get a record of the concentration of sugar present.

When the urine test is positive, it is wise to attempt the identification of the contained sugar. Most laboratories will find it easiest to begin the identification by fermentation with baker's yeast. In the fermentation test, glucose and fructose will be destroyed; lactose and pentose will be untouched; galactose may break down a little. Castellani and Taylor[33] advised that special pure strains of yeast be utilized, but in practical experience ordinary commercial baker's yeast is dependable and satisfactory. After the fermentation, centrifuge or filter the urine to be rid of the yeast, then repeat the quantitative reduction test. The difference between the 2 quantitative determinations after allowing for dilution by the yeast emulsion represents the fermentable sugar. If the second determination shows that more than a trace remains unfermented, the presence of two different sugars is indicated, and then each must be separately identified.

Differentiation of fructose from glucose, both fermentable, if no polarimeter is available (and few clinical laboratories possess one), is effected by the Lasker and Enklewitz[85] technique of placing a mixture of urine and Benedict's qualitative reagent in a water-bath for 10 minutes at 50 to 60° C. Fructose, being a ketose, reduces quickly at this temperature, whereas glucose does not. One may apply also the Seliwanoff resorcinol test for ketoses or search for the insoluble methyl fructosazone. If the sugar is fermentable and the fructose tests negative, the sugar may be presumed to be glucose itself. For positive identification of glucose, if desired, prepare the osazone or measure the rotation of polarized light.

Of the non-fermentable sugars, pentose will give a positive reaction with Benedict's solution at 50° to 60° C. in less than 10 minutes, or when the mixture is left standing at room temperature for 3 hours or longer. The mucic acid test denotes galactose or lactose (these two can be differentiated by the phlorglucinol reaction). The Bial HCl-orcinol-ferric chloride test, the aniline-acetate reaction and that of Tauber[150] will indicate pentose. For lactose the Rubner test is insensitive and misleading, according to Edson;[50] the phenylosazone technique is best. The osazone tests, generally speaking, are very helpful when clear-cut, but unfortunately many urines contain mixed sugars and give rise to atypical complex crystalline forms. For critical description of these and more technical

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methods, the reader is referred to standard texts on biochemistry, to Hawk and Bergeim's[76] "Physiological Chemistry," to Reiner's "Manual,"[127] and to Edson's constructive comments.[50]

Differentiation and exact identification of the sugars requires experience. It may be necessary to check the procedures themselves by control tests with known sugars added to urine, while realizing that commercial preparations of the individual sugars themselves are not always wholly pure. In practical work, the fermentation and temperature reduction reactions may be as far as one is able to go, leaving the more specific and difficult tests to specially interested laboratories.

Exton[56] has stressed that it is unsafe to assume that glucose, or indeed any other sugar, is the cause of a positive reduction test, especially when concentrations run 1 % or less. He devised an ingenious method for identifying the various reducing substances, applying the universal Electro-Scopometer to the measurement of their distinctive reduction rates when mixed with a di-sodium-di-nitro-salicylate reagent. His studies emphasize the motley variety of non-glucose reducing substances which may appear in urine, and the importance of the as yet unexplored field of the urine sugar mixtures which are often unexpectedly met.

Reference may be made in passing to the new powder reagents which have lately been developed for the rapid detection of sugar in urine.[73,144] Consisting essentially of bismuth salts already mixed with other reagents, these powders, commercially available, change color in the presence of reducing substances. They require almost no equipment and are stated to be accurate and selective.

Most children when in good health can ingest an abundance of carbohydrate without developing alimentary glycosuria. In an unpublished study of the 1-hour 2-dose glucose tolerance test (Exton-Rose) in childhood, Du Swun Deh[48] found, with 90 youngsters ranging in age from early infancy to 11 years, that 2 test doses of 1.75 gm. per kilo body weight given after an overnight fast did not in any instance spill into the urine to give a positive reduction test.

Alimentary Melituria. Any of the sugars, if fed in inordinate amounts, will overflow into the urine. Thus fruits or fruit juices when taken in excess gives rise to pentosuria or fructosuria, occasionally in combination; cane sugar produces sucrosuria or glycosuria; candy induces glycosuria, maltosuria or dextrinuria; excess lactose or galactose result in lactosuria or galactosuria. Alimentary melituria of this sort, of dietary origin, are transient and harmless. They are seen most often during febrile illness because fruit juices and other carbohydrate-rich foods are forced at a time when the physiologic functioning of the small intestine and liver is not at its best, and because urinalyses are commonly done at these times. Hospitalized patients, while receiving glucose solutions by vein, usually have glycosuria. Folin and Berglund[64] have described the escape into the urine of appreciable amounts of dextrin derivatives following the ingestion of dextrins and caramelized starchy foods. Foods containing pentosans—among them, grapes, cherries, strawberries, blackberries, prunes, wine, fruit juices and fruit-flavored soft drinks and beer—can provoke a transient excretion of xylulose or arabinose into the urine.

The transient character of such melituria in children is brought out by Mihara.[110] Of 1648 children, the incidence of specimens positive for reducing substances was as high as 5.8 %. Unfortunately, the only available summary of Mihara's paper, that of Kato, fails to give the state of health of these children, but the high frequency of positive reactions and asso-

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ciated acetonuria implies that the specimens were collected in a hospital for sick children. On osazone identification, glucose was found to occur most frequently (86%), the other sugars being lactose, galactose and maltose. The incidence of positive specimens was higher in the younger age groups, and during the summer months. Acetonuria was nearly as common as melituria. No significant relationships were noted between dietary habits or types of disease and melituria. Sugar tolerance tests on 4 children resulted in practically normal curves. Significantly, in follow-up urinalyses, the reactions for melituria persisted in but a few cases.

When the urine of a sick child with acidosis exhibits both ketone bodies and alimentary melituria, the physician may suspect and hint at the possibility of diabetes to the parents.[7] Needless to say, the mere mention of such an idea would excite great anxiety. Inasmuch as the great majority of episodes of glycosuria combined with ketonuria in acute illness during childhood are non-diabetic and of no permanent significance, the doctor should not voice his suspicion of mild or beginning diabetes until it becomes confirmed either by events of the next few days or by diagnostic studies made after the subsidence of the acute symptoms.

Renal Glycosuria. This diagnosis is made when there exists a harmless, chronic, non-progressive excretion of glucose with no symptoms of diabetes and with no hyperglycemia during fasting or after a meal. The quantity of sugar excreted may either fluctuate with variations in carbohydrate intake or be largely independent of the diet. The glucose tolerance curve is normal, as is the fat metabolism. There are no symptoms, and treatment is not needed. The injection of insulin with the subsequent reduction of blood sugar does not eliminate the glycosuria. The typical picture probably never changes to that of diabetes mellitus, but patients must be watched for some years before the differentiation can be established beyond doubt. Similar disturbances are often found in relatives of the patient. Marble[100a] suggested that the respiratory quotient before and after a carbohydrate meal could be applied to prove the ability of the patient to store and utilize carbohydrate in a normal fashion, though the failure of mild diabetic patients to show such impairment under certain conditions[125] blocks the use of this determination as a criterion for differentiating mild diabetes from non-diabetic glycosuria. Subjects have been followed for as long as 20 years[100b] without ever demonstrating any signs of diabetes or other disease attributable to the glycosuria.

John[80] objected to the adjective "renal" because "all glycosurias are renal in origin, depending upon the renal threshold as well as the glycemic level." The term normoglycemic glycosuria utilized by Powelson and Wilder[122] is more logical, but as with so many other ill-fitted names in medical terminology, "renal glycosuria" is sustained by too great a weight of tradition to be easily displaced. According to Marble, who reflected Joslin's[100b] views, the designation of renal glycosuria should not apply when the excretion of sugar is inconstant or intermittent, or if the morning fasting specimen contains no sugar. Fischer[61] disagreed, stating that the question as to whether the glycosuria is continuous or intermittent depends solely on the threshold level of a particular patient. Fischer described 2 children who conformed to all the accepted criteria for renal diabetes save that in one the threshold for excretion was approximately 135 mg., and in the other, somewhere between 90 and 135 mg. Both were studied for a sufficient length of time to establish the non-diabetic nature of their disorder.

The hereditary character of renal glycosuria has been commented

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on by all recent writers; in fact, most affected children are detected in family surveys made after an adult member has been found with the complaint. For example, Brown and Poleshuck[26] discovered 4 cases in 3 generations of one family. The grandchild, aged 10, like the other members, exhibited no symptoms or signs of diabetes mellitus, though urine specimens examined over a year all contained glucose. Following 60 gm. of glucose, by mouth, his blood sugar curve remained nearly horizontal, rising from a fasting level of 93 mg. per 100 ml. to 111 mg. after 30 minutes, and dropping to the base level by 1 hour. The quantity of sugar found in the urine was in trace amounts (0.03 to 0.5 mg. per 100 ml.); the more adult members of the family excreted larger quantities. On the other hand, there are cases such as Skole's[139] with a negative family tree. This patient interestingly was given 20 to 50 units of insulin daily for several weeks with no effect on the output of urinary sugar, even on the one occasion when he approached insulin shock. The concentration of sugar in the urine in 7 of 933 children with renal glycosuria ranged from less than 0.3% to 5%.[159]

Whether the glycosuria is present at birth or begins later on, has not been fully settled. The youngest known case was the month-old patient of Landabure.[84] There is some sex linkage: males are affected more frequently than females. The escape of sugar seems to persist continuously for the rest of life.

In adults, symptoms consequent to hypoglycemia were described by MacPherson.[98] These were minor degrees of faintness and weakness ascribed to a low fasting blood sugar level, and similar but more severe attacks attributed to relative hyperinsulinism following rapid loss of sugar in the urine. No reports of children having such episodes have been encountered.

Lead Poisoning. In studies carried out on a child having lead poisoning with glycosuria by Goettsch and Mason,[71] the height of the blood sugar was consistently normal or lower than normal, and the urinary concentration of sugar remained relatively constant irrespective of the diet. The glycosuria persisted for 5 weeks, the concentration of urinary sugar diminishing as convalescence progressed. The authors suggested that the condition in lead poisoning may be classified as renal glycosuria secondary to intoxication of the kidney, and supported the suggestion by a survey of 8 cases of lead poisoning with glycosuria in children. In 5 cases the blood sugar values were normal; in 3 others in which dextrose tolerance curves were obtained the curves were not of the diabetic type. Glycosuria did not seem to alter the prognosis of the lead poisoning in these patients.

Intermittent Glycosuria. A puzzling phenomenon is the metabolic state in which glycosuria recurs intermittently for a time and then ceases altogether. Bayer and Davis[15] described 9 such boys, aged 2 to 10.3 years, who because of recurrent glycosuria, were at first suspected of having early diabetes mellitus. However, their dextrose tolerance tests were normal at that time and there were no evidences of diabetes on reëxamination 2 to 11 years later. The diagnoses made at the time of recheck were: normal, 6; unclassified glycosuria, 2; hyperglycemia after ingestion of glucose, 1. The rarity of this type of case is evidenced by the fact that collection of these 9 took 15 years, during which period some 50 children passed through the pediatric ward at the Stanford Univ. School of Medicine for study for possible diabetes mellitus. Bayer and Davis commented that, though the ultimate diagnoses of these glycosuria cases cannot be

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foretold, it is unlikely that more than 1 or 2 would ultimately develop diabetes.

Diabetes Mellitus. The relationship between glycosuria and diabetes mellitus needs no discussion here. But one should remember that childhood diabetes may commence insidiously, that diabetic glycosuria at its beginning can be inconstant and intermittent. Mid-morning or mid-afternoon specimens may contain some sugar, perhaps but trace amounts, whereas those on rising in the morning may be entirely negative; hence it is wise to study thoroughly any child who exhibits glycosuria, even if positive specimens alternate with negative ones. A sugar tolerance curve after feeding carbohydrate for a few days is mandatory whenever there is the least uncertainty over the cause of the glycosuria. Non-elevated fasting specimens alone cannot be depended upon to exclude diabetes, since children with mild diabetes often may have normal or high normal levels when not taking food.

Transitory diabetes mellitus is a rarity, described but a few times. Söderling's[142b] questionnaire, sent in 1935 to pediatric clinics all over the world, asked, among other questions, for information regarding completely subsided cases of diabetes in childhood, since the onset of insulin therapy. Only 2 spontaneously cured cases were submitted, 1 from Birmingham, England, and 1 from Toronto, Canada. Söderling[142a] himself described a 5 year old child who recovered from a transitory attack of acute diabetic coma in association with pneumonia.

Fykow[66] reported a 2 year old boy with pneumonia, whose rapid breathing persisted after the temperature fell to normal. The urine at first contained acetone solely; sugar did not appear until 4 days later. The blood sugar rose to 312 mg. per 100 ml. A course of insulin treatment cured the patient's symptoms, though 4 months later the sugar tolerance curve was still abnormal, with a reading of 148 mg. 3 hours after glucose. Several other members of the family were found with abnormal blood sugar curves. Fykow suggested that this child with transitory diabetes would probably display permanent diabetes later in life, and advised a diet low in carbohydrates as a precautionary measure.

Essential Pentosuria. This has been defined as a "hereditary abnormality of metabolism characterized by continuous excretion of small amounts of pentose in the urine, unaffected by alterations in the diet" (Edelman and Reiner[49]). These authors state that more than 170 cases have been reported, and refer to Blatherwick's estimate of an incidence of approximately 1:50,000 in the general population. The pentose excreted seems to be consistently xylulose. Under ordinary circumstances the daily output of pentose does not fluctuate either after changes in the carbohydrate or protein content of the diet or after periods of violent exercise followed by prolonged rest in bed, but does increase after feeding of its precursor *d*-glucuronic acid. On the grounds that identification was inadequate according to modern standards, Edelman and Reiner question seriously the reports from the first decade of this century that pentosuria occurs frequently in persons with severe diabetes. Many of the more contemporary workers, Marble,[100b] for example, have searched for pentose in the urine of large numbers of diabetes patients with scant success.

The disorder appears to be a harmless metabolic phenomenon which is congenital and persists unchanged throughout life. Many patients have been Jewish. No special pathogenetic significance can be attached to cases which may be identified during infancy or childhood, as compared with others not discovered till later in life.

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Fischer and Reiner[62] conducted metabolic studies on 4 children aged 2 to 10 years having pentosuria. The non-fermentable reducing substances of their blood were not increased, and dextrose tolerance and blood pentose curves following ingestion of test amounts of these sugars were normal. There were no essential differences between the absorption and the excretion of pentoses in normal controls and in pentosuric children. Sunderman[147b] found, on tracing the family of an 8 year old girl with the condition, that 2 of her 3 brothers and probably the mother were also affected. When Enklewitz and Lasker[54a] fed 5 gm. of xylulose isolated from his own urine to a man with pentosuria, the rise which resulted was only 0.5 gm. more than the usual daily excretion. Thus the origin of the xylulose which appears in the urine of pentosuria remains unknown.

"Patients with essential pentosuria require no treatment except for the reassurance that they do not have diabetes mellitus."[54b] This is well illustrated in the cases reported by Enklewitz and Lasker. A pair of twins, brother and sister, were studied for diabetes when 11 years old because of the daily excretion of 1.5 to 3 gm. of sugar in the urine. Seventeen years later they were still asymptomatic; the urine sugar, still persisting, was identified as xylulose.

Fructosuria. Fructosuria, known also as levulosuria, has been recently reviewed by Sachs, Sternfeld and Kraus,[134] who listed some 55 cases described since 1876 and added 2 others, children, personally observed. They commented that in 16 of the cases the data obtained was inadequate to fully establish the diagnosis. As regards age, 15 of the entire group were below 17 years of age when first studied, and 5 were younger than 7 years. The condition is clearly constitutional, and can be presumed to continue uninterruptedly from infancy throughout adult life.

In essential fructosuria, according to Silver and Reiner,[138] the sugar is always present in the urine except when the patient is given a fructose-free diet. The identity of the sugar can be established by its levorotary properties, the positive Seliwanoff test when the urine is acid, complete destruction by yeast fermentation, demonstration of a methylphenyl fructosazone, and normal dextrose tolerance curve. The sugar content should be the same when measured by optical rotation and by yeast fermentation.

Sachs, Sternfeld and Kraus[134] suggested that in these cases the mechanism for the fructosuria lies in the failure of ingested fructose to be broken down to lactic acid. In essential fructosuria, the respiratory quotient changes but slightly from the fasting value after the ingestion of fructose, and the level of lactic acid in the blood does not increase. In normal subjects, on the other hand, as shown by Deuel,[40] Bachmann and Haldi,[11] and Rynbergen, *et al.*,[133] the ingestion of fructose results in an increase in the respiratory quotient to unity or above, the rise occurring more promptly and the quotient rising higher than when dextrose is given. This phenomenon seems to be related to the normal tendency for fructose to induce a greater accumulation of lactic acid in the blood than does dextrose. Hence Sachs *et al.* propose that, when a normal person takes fruit or cane sugar or honey, some 80% of the ingested fructose becomes converted to glycogen while the remainder breaks down to lactic acid; whereas when an individual with essential fructosuria ingests these foods, some 10 to 20% of the ingested fructose fails to become metabolized, and instead is excreted intact in the urine. "The abnormality may lie in the failure or lack of some specific enzymatic action, the site of which has not yet been determined but which may be in the intestine, the blood or the liver."

Debré *et al.*[39] described a 6 months old infant with furunculosis, who for 10 days exhibited a pronounced fructosuria while being fed sweetened condensed milk rich in sucrose. The fructosuria disappeared when the diet was changed to one low in sourse. Four months later the fructosuria could not be reëstablished by liberal feeding of fructose and sucrose. Evidently during the period of infection this infant's liver was not functioning adequately; it failed to convert into glycogen all the fructose brought to it from the site of sucrose splitting in the intestine.

Galactosuria. A few cases with malnutrition and galactosuria have been reported, the one of Mason and Turner[103] being the most intensively studied. This infant, followed from 6 months to 3 years of age, did not gain normally so long as the diet contained milk. He showed marked enlargement of the liver, slight enlargement of the spleen and superficial lymph nodes, positive reaction to the van den Bergh test, secondary anemia, osteoporosis of the bones and protein and galactose in the urine. Removal of milk from the diet resulted in the disappearance of sugar and protein from the urine, decrease in the size of the liver and spleen, disappearance of the other findings and a rapid gain in weight. The curves for blood sugar after the ingestion of dextrose and levulose were within normal limits, but those for lactose and galactose were abnormal as a consequence of pathologic increases in the level of blood galactose. Mason and Turner suggested that the primary trouble was a lesion or functional disturbance in an otherwise normal liver, impairing the ability of this organ to convert galactose into glycogen, and that the derangement in the other tissues was the result of relative starvation due to the continuously low level of blood dextrose.

In addition to the above case, in recent years Fanconi[58b,c] described a 9 year old boy with familial neurofibromatosis, zonular cataract and galactosuria, and Lescovar[90] a 4 week old galactosuric infant who expired at 4 weeks of sepsis and cholangitic cirrhosis of the liver. It is likely, however, that the incidence of the disorder is higher than indicated by the paucity of published reports. Every child suspected of having von Gierke's "glycogen disease" with recurrent melituria (*vide infra*) should be studied carefully for galactosuria.

Mason and Turner's patient, when given 25 gm. of galactose in a 7-hour tolerance test, excreted only 6.64 gm. during the period, evidently storing or catabolizing the difference. Fanconi's patient, on the other hand, excreted 1 gm. in the urine after being given 2 gm.; after 6 gm. he excreted 5.2 gm.; the larger dose caused a rise of blood sugar to 466 mg. per 100 ml. and symptoms of apathy and weakness. Thus the metabolism of galactose in such cases may be imperfect, but is not wholly inadequate.

No cases of urinary elimination of the disaccharide lactose, such as occurs at times in women during pregnancy or later during lactation, were found reported in the 10-year period covered by this Review.

Sucrosuria. A 7 months old infant with saccharosuria (sucrosuria) was reported by Reiner and Weiner.[128] The saccharosuria occurred both when saccharose itself was given in excess and when it was fed in lesser amounts along with other sugars, which appear to compete for prior digestion and absorption. Thus the saccharosuria appeared to be alimentary in origin. Reiner and Weiner theorized that, in the presence of infection, either enteric or parenteral, increased intestinal permeability may result in absorption of disaccharides. In their child, the disturbance was demonstrated at the ages of 7 and 18 months when certain combinations of carbohydrates were given. Elmer, Krasowska and Ptaszek[52] describe

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an adult case, and state that there are only 2 other cases in the literature (both adults) besides theirs and that of Reiner and Weiner. They discuss the physiologic sucrosuria which follows the taking of large amounts of cane sugar, commenting that after 150 to 250 gm. of cane sugar are taken by mouth the urinary excretion will not exceed 1% of this amount, the remainder being hydrolyzed in the intestine. Masserman[104] has shown that 90 to 100% of intravenous sucrose will be excreted.

It should be remembered that disaccharides will not react with Benedict's solution unless the urine is first acidified and boiled to hydrolyze the sugar into its component hexoses.

Glycogen Storage Disease (von Gierke). The clinical and pathologic data on all cases reported as glycogen storage diseases were collected and analyzed critically by Mason and Andersen.[102] They succeeded in classifying the cases into 5 separate types, each with a different fundamental defect. Of the 34 cases of the hepatomegalic type in their collection, it has been pointed out[99] that urinary sugar was present in only 2 of the 23 cases in which tests for sugar in the urine were reported. Manter and Bowman[99] described another instance, a 14 month old boy, in whom glycosuria was intermittently present. In this patient the glycogen of the liver apparently was not abnormal, but the glycogen metabolism was deranged as shown by ketonuria, deficient storage of ingested dextrose, inability to mobilize dextrose from large amounts of glycogen in the liver when epinephrine was injected, and failure of hepatic glycogenolysis after death. Manter and Bowman explained the glycosuria in terms of a low renal threshold, while suggesting that it may have been related in some way to the glycogen found in small amounts in the epithelium of the renal collecting tubules after death.

The Fanconi Syndrome. A number of cases of refractory rickets have been reported in which non-diabetic glycosuria was a prominent associated feature. This syndrome, first separated from the larger group of so-called renal rickets by de Toni[41] in 1933 and Fanconi[58] in 1936, is characterized in general by severe intractable hypophosphatemic rickets, renal glycosuria, polyuria, and acidosis with extreme reduction of the serum bicarbonate. It appears to be congenital in origin. In the case of McCune, Mason and Clarke[106] the protein nitrogen and urea of the blood were normal, but the urine contained large amounts of protein, ammonia, lactic acid, betahydroxybutyric acid and amino acids. A balance study revealed excessive excretion of phosphorus and calcium by the kidneys. The metabolism of sodium, chlorine and magnesium appeared unaffected. Treatment with 5000 U.S.P. units of vitamin D daily for several weeks caused no evident improvement.

On reviewing the reports on record, McCune *et al.*[106] found 28 seemingly related cases in infants and children and 2 others in adults in whom rickets was replaced by osteoporosis. They concluded that the Fanconi syndrome, with its combination of rickets, hypophosphatemia and renal glycosuria is not a sharply definable clinical entity, but without perceptible demarcation merges with classic hyperphosphatemic renal rickets on the one hand, and with the poorly understood process known as cystine rickets on the other. They hypothesized that the fundamental defect is a diminished ability of the renal tubular epithelium to resorb dextrose, amino acids and phosphate from the glomerular filtrate. To neutralize the undue amounts of organic acids, large quantities of ammonia and mineral cations are excreted, with consequent depletion of the total base of the body fluids. Recurrent hypoglycemia was thought to be responsible for the excretion

of betahydroxybutyric acid, and the presence of lactic acid was ascribed hypothetically to a dyscrasia of either the renal tubules or the liver.

According to McCune *et al.*, the concentration of reducing substances in the urine can vary between a trace and 4 or 5%. The excretion of sugar is characteristically continuous, at least in patients with the more severe forms of the syndrome; though it may be intermittent and disappear for considerable periods of time. On investigation, the reducing substance is usually found to be dextrose. However, Lignac's[94] patient first excreted a pentose and later a substance, the osazone of which melted at the temperature of lactosazone; Gittleman and Pincus[70] reported dextrose and fructose in nearly equal concentrations; van Creveld[153a] ascribed part of the reducing capacity of his patient's urine to glycuronic acid with dextrose also present in concentrations of 1 to 2%. The fasting blood sugar level ranged from 48 mg. to 160 mg. per 100 ml. The glycosuria varied in intensity with changing levels of blood sugar but was characteristically present at all times, even when the blood sugar was low. During the oral administration of dextrose for test purposes, Debré's[38] patient became restless and pallid and then lapsed into fatal coma, and 2 of Fanconi's[58] patients were rendered extremely uncomfortable but survived.

In most cases the volume of the urine was moderately increased. Despite the large volume of urine, McCune *et al.*[106] noted that the specific gravity was frequently high, due to the presence of sugar, protein and other solutes. Proteinuria of moderate degree was a consistent phenomenon; casts, leukocytes and epithelial cells were often present. Microscopic hematuria was reported occasionally. Despite the demands made by acidosis, the pH of the urine was frequently 6.5 or higher, though McCune's case occasionally assumed values as low as 4.8. High urinary concentration of ammonia, and especially large quantities of phosphates and organic acids were always encountered when searched for.

4. **Sulfonamides.** The pathologic changes in the urinary tract resulting from administration of sulfonamide drugs was thoroughly summarized in a review published in this Journal several years ago by Peterson and Finland;[119] not much new has been learned since then. Direct renal damage with sulfanilamide and sulfadiazine is quite uncommon, whereas sulfapyridine and sulfathiazole exert the largest share of their toxic effects upon the kidney. The lesions in the urinary tract are produced mainly by crystalline sulfonamides which precipitate out, mixed with blood and amorphous matter, anywhere along the tract from renal tubules to bladder. Hemorrhages follow, the urine flow becomes obstructed, the passages dilate above the obstruction, and the kidnesy grow large and edematous. Or there may be direct necrotoxic changes, with glomerular reactions and epithelial degeneration of the tubules. In some instances, both kinds of injury have been recognized in the same kidney.

Crystalluria and Hematuria. The specific solubility of the various sulfonamide compounds and their acetylated derivatives determines in large measure the frequency and the quantity of the crystals which appear in the urine. *Sulfadiazine* and *acetyl sulfadiazine*, which are the most soluble, are the least likely to give rise to urinary tract disturbances. *Acetyl sulfathiazole* is much less soluble in urine than is the *free* form, and both substances are slightly more soluble in alkaline than in acid urine. This difference did not seem of sufficient magnitude to Peterson and Finland to warrant alkalinization of the urine as a precaution against renal complications during sulfathiazole therapy, whereas Sunderman and Pepper[148] did make that recommendation. With *sulfanilamide*[35,59,101] the

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acetylated form is one-third as soluble as is the free drug under similar conditions. *Sulfadiazine*,[68,130] *sulfamerazine*[69] and *sulfamethazine*[69] and their N_4 acetyl derivatives increase markedly in solubility with a rise in pH from 5 to 8; *sulfapyridine* and *acetyl sulfapyridine* do not.[119] All observers agree that when pH conditions favor solubility, or when there is a good diuresis, the crystalluria and hematuria are usually inhibited, whereas with unfavorable urinary pH and scanty urine the likelihood of such difficulties becomes enhanced.

Urinary crystals and renal stones in patients taking sulfadiazine are about 93% acetyl sulfadiazine, and the solubility of the acetyl portion of these urinary crystals is similar to that of pure acetyl sulfadiazine. Clinical studies suggested by these solubility findings[148] revealed the incidence of crystalluria to be 27% in 172 acid urines and but 1.4% in 147 neutral or alkaline urines. It follows from these observations that patients receiving sulfadiazine be given alkali along with it, in order that the urine be kept neutral or alkaline and the precipitation of sulfadiazine compounds in the urinary tract be prevented. This procedure seems especially necessary when large doses of this drug are being given over a protracted period of time. The dosage of alkali can be regulated by watching the pH of the urine; enough should be administered to keep the pH at 7.5 or higher. Nitrazine paper is helpful for this purpose; with children sick at home the parents can be instructed as to its use. When small doses of sulfadiazine are given for but a few days the precaution is less essential.

The crystals observed in specimens often form and settle out as the urine stands in the bottle at room temperature. From the standpoint of urinalysis, therefore, the discovery of crystals does not necessarily hint at internal crystallization unless the urine is warm and freshly voided, or unless red cells are also present. If they appear under these circumstances, one should be alert for crystal deposit and calculi formation within the urinary tract. Precautionary fluids should be forced and alkalis given to assure the pH of optimal solubility in the urine. The drug should be discontinued and urologic procedures resorted to if indicated.[79]

Hematuria is the danger signal. Children receiving any of these drugs in large quantities or for more than a few days should have a microscopic urinalysis every 2nd day, in order to detect renal irritation in its beginning stages. In adults, according to Smith,[140] the frequency of sulfonamide hematuria is as follows: sulfapyridine, 2 to 3%; sulfathiazole, 2 to 3%; sulfadiazine, 0.5 to 1%. Oliguria, too, has occurred in a small percentage of cases receiving sulfapyridine, sulfathiazole or sulfadiazine. Of 53 children with assorted infections treated with sulfathiazole by Dowrie and Abramson,[45] only 1 showed hematuria in daily urinalysis; 2 of 54 children receiving sulfadiazine exhibited hematuria. The experience of Winters and Janney[161] is in contrast with the above low figures. Of 90 children hospitalized and given sulfadiazine for infectious diseases of wide diversity, 12 had erythrocytes and 18 had both sulfadiazine crystals and erythrocytes in the urine. These toxic effects cleared when the dosage was lowered.

The drug sulfamerazine is too new for the publication of reports on its toxicity in the early years of life, but to judge from personal experience the incidence of urinary findings would seem to be at least as common as with sulfadiazine. On comparing 428 adult patients treated with sulfamerazine against 900 controls treated with sulfadiazine, Dowling *et al.*[44] found the incidence of renal calculi higher in the sulfamerazine group when identical doses of each drug were given.

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The concentrations of the various sulfonamides in freshly passed urine are higher than can be secured by dissolving the same substances in water or urine *in vitro*. It has been suggested that these drugs may be excreted as highly soluble glucuronates or related substances. Lehr and Antopol[88] proposed that protective colloids in the urine serve to inhibit the sulfonamide precipitation. They found that the comparatively insoluble acetyl derivatives which form in the body from sulfapyridine, sulfathiazole and sulfadiazine, if analyzed as urinary crystals, showed a markedly depressed melting point; on recrystallization the solubilities approached or reached those of the pure synthetic compounds.

The Wood Fiber or "Lignin" Test. A new "easy, rapid and reliable" test for the presence of sulfonamides in urine has come into wide use within the past 2 years. Originally proposed by Hallay,[75] favorable reports soon followed by Bogen,[23] Kawaichi[83] and Hubata,[78] and the Reviewer can sponsor its reliability from extensive personal experience. The essence of the test is the production of a yellow or orange color when any of the sulfonamides, which all contain the aniline group, react with wood fiber in the presence of acids. To perform the test, one acidifies with a few drops of 4% HCl a fragment of newsprint paper, paper toweling (not rag paper), sawdust, or tongue depressor, adds a few drops of urine, and watches for the appearance of the distinctive color. Kawaichi states that the color is yellow when the concentration of the drug in urine is 100 mg. or less; orange when above 100 mg.; and that there is danger of sulfonamide concretions when the concentration is above 100 mg.

In our experience the color change reaches its visible maximum at about 70 to 80 mg. free (unacetylated) sulfonamide. It is easy to establish that this color reaction is produced only by the free form of the sulfonamides, with the acetyl derivatives playing no part.

The physician prescribing sulfonamides will feel diminished anxiety regarding danger of calculus formation if the urines of his patients are kept sufficiently dilute to yield a yellow rather than orange color with the wood fiber test, and are also at the pH of optimal solubility (above pH 7 with sulfadiazine) when checked with nitrazine or litmus paper.

5. **Pigments.** The color of urine normally varies from pale to dark amber, the shade depending chiefly upon the content of urochrome. Drabkin[46] found the output of this pigment to be a constant quantity from day to day in state of health, but augmented by fasting, fever, hyperthyroidism, and all factors which stimulate endogenous metabolism. Normal urine may also contain trace amounts of hematoporphyrin, uroerythrin and urobilin.

Under abnormal circumstances, other pigments may escape from the body fluids into the urine. Some of these, such as anthocyanin, result from diet or medication; some, such as urobilin, hemoglobin and its derivatives, and melanin, indicate systemic disease; and others, such as the porphyrins and homogentisic acid, are manifestations of congenital errors of metabolism. Selected for consideration here are comments from recent noteworthy papers.

Anthocyanin. The red pigmentation of the urine which sometimes follows the eating of red beets is due to anthocyanin, the principal pigment of the beet, and may vary from light to dark red. Matheson[105] and Poole[120] have each described cases, and most pediatricians are familiar with its occurrence. The pigment can be quickly differentiated from hemoglobin by adding alkali, such as potassium hydroxide or sodium hydroxide solution, to the urine. The color becomes deep yellow when alkalinized,

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and will revert to the original red when acidified once more. No one knows why anthocyaninuria is infrequent when beets are so common in the diet of children.

Urobilin. According to Josephs,[81,82] the normal child excretes the bulk of his urobilin in the stools, the urine urobilin constituting but 5% of the total daily excretion. In infancy and early childhood the total 24-hour urinary excretion of urobilin can be expected to be but 1 or 2 mg.; in preadolescence and puberty, 4 to 5 mg. These small amounts escape detection by the usual tests. When there is anemia of hemolytic origin, however, the total excretion of urobilin increases strikingly, often reaching 20 to 30 times the normal. The urine then becomes positive for urobilin, though the ratio between stool and urine urobilin remains about the same as in normals. Only in cases of extensive liver damage did Josephs find the proportion of urinary to fecal urobilin to be elevated, attaining ratios of 10 to 20% or higher.

The term "urobilin" covers a number of substances of unknown composition giving fluorescence in alcoholic zinc acetate. On first appearing in the urine these substances exist in the chromogenic or urobilinogen state, but become oxidized on exposure to air, and after a few hours change to urobilin itself. From the standpoint of the laboratory technician, the standard test for urobilinogen—that of Ehrlich—is easier to perform than that for urobilin. Specimens to be tested for urobilinogen should reach the laboratory fresh, within the first few hours of passage, before this change occurs. Because relatively small amounts reach the urine, quantitative tests for urobilinogen meet no special clinical need; when information regarding total urobilin excretion is desired, the stool analysis yields adequate information. In searching for the presence of urobilin in a patient with possible undue hemolysis, it is wise to repeat the test daily for several days, since excretion of excess urobilin may be erratic and irregular.

Homogentisic Acid. Alcaptonuria is an outward manifestation of a very rare congenital anomaly of protein metabolism in which homogentisic acid is excreted in the urine. This substance, colorless itself, darkens on standing, due to oxidation. It reduces Benedict's solution, but fermentation tests for sugar are negative. In enuretics the bed linens often turn dark as the urine undergoes ammoniacal decomposition. Abbott[1] described the condition as it occurred in 2 Negro siblings, the first instances to be reported in the American Negro. Addition of 10% sodium hydroxide solution to the clear urine resulted in a brownish black ring at the surface which gradually penetrated downward, ferric chloride solution caused a transitory blue color with each drop, and reduction of silver lactate and of ammoniacal silver nitrate proceeded rapidly at room temperature. The concentration of homogentisic acid was found to be 4.4 to 5 gm. per liter, and the homogentisic acid to nitrogen (H:N) ratio ranged from 45.1:100 to 53.5:100. It was possible to precipitate out the lead salt of homogentisic acid from the urine of both children.

Of the numerous other cases recently reported, that of Lelkes[89] is exceptional in that the mother of his 3 months old affected infant had also had alcaptonuria as a child, and this had ceased spontaneously when she became 12 years of age.

Porphyrin. Porphyria, a more descriptive term than porphyrinuria, is a constitutional state marked by the excretion of porphyrins either in greater than physiologic amounts or in kinds not normally demonstrable. In the congenital variety, according to Dobriner and Rhoads,[43] the classical

manifestations consist of excretion of large amounts of porphyrin, discoloration of the teeth and bones by impregnated uroporphyria, and sensitivity of the skin to light in the spring and summer. Blistering of the exposed areas of the face and extremities is observed, and the lesions heal with scar formation, followed in many cases by deformity of the affected part. Turner and Obermayer[153] were able to find but 86 cases on record up to 1936. Only one-half of these had had symptoms beginning prior to puberty.

The urine may vary from pale pink to red to almost black, though usually Burgundy red. Often the urine when passed is a normal yellow, but darkens later when exposed to light, sunlight being most effective. For details concerning this unusual condition the reader is referred to Turner and Obermayer,[153] Dobriner and Rhoads,[43] and Watson.[156] The pathogenesis of this disturbance is not known. The pigments in the urine are chiefly coproporphyrin Type 1 and uroporphyrin Type 1, as well as some brown urofuscin. If present in quantity, they can usually be identified by study of the absorption spectra. Guild[74] was able to prevent active symptoms in one patient by liver extracts in large doses.

6. **Findings in Newborn and Premature Infants.** The past decade has made but few contributions to general information concerning the character of the urine in the neonatal period. The most extensive report on newborns is by Tausch,[151] who reviewed much of the earlier literature and described his own observations in detail. Tausch catheterized some 4000 newborn infants promptly after delivery and was able to secure urine specimens in 2837, the remainder having presumably voided while passing through the birth canal. In quantity the urine varied up to 44 ml., averaging 5.7 ml. There was no sex difference and no relationship between duration of labor and quantity. The color varied from colorless to deep yellow, 27% being free from color. The specific gravity had a mean of 1.0097 and a range of 1.004 to 1.019. Specific gravity showed a definite relation to body weight, the means for increasing weight groups progressing from 1.0072 in those under 2500 gm. up to 1.0112 for those between 3500 and 4000 gm. In reaction, 1794 were acid, 164 alkaline, and 879 neutral. A review of the literature was given to show that proteinuria is common in the first day of life. The author's figures showed 403, or 14.21% of the 2837, positive for protein, 215 (7.59%) markedly so. Tausch failed to find any significant correlation between proteinuria and kidney disease in the mother, or to duration of passage through the birth canal. Infants delivered by Cesarian section showed approximately the same incidence of proteinuria as those born in the usual fashion. In only one instance was the urine grossly bloody; 32 had microscopic red cells, 59 had leukocytes and 8 had casts. Bile was not present in any case. Although the literature reviewed showed that reducing substances occur occasionally, the author failed to find any specimens containing sugar in his series, even in the operative and difficult labor cases.

The above observations on the composition of what may be termed urine accumulated *in utero* can be compared with those of Faerber[57] on postnatal urine. On comparing clinical appearances with weight curves, fluid intake, body temperature and protein content of the blood in 30 newborns from 1 to 10 days old, Faerber found that albuminuria and excretion of casts and leukocytes ran parallel with dehydration. These positive findings disappeared after the fluid intake had become about 10% of the body weight.

Allyn and Allyn[6] have reported on the urinary findings in the newborn

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given ammoniated mercury rubs for the prevention of impetigo. In a total group of 220 infants, tested on the 5th and usually again on the 7th day of life, a positive sugar reaction was found 4 times. In addition, 18 specimens showed "trace" amounts of reducing substances. Of these, 132 babies received inunctions of $3\frac{3}{4}$ ammoniated mercury, and 88 served as controls. Of the group receiving the rubs, 18% had protein, 63% had leukocytes, and 5% a few red cells. Of the controls, only 4% had protein, 28% had leukocytes and 1% had a few red cells. These differences were interpreted as indicative of mild renal irritation from the ointment. The data are informative also in that the findings in the controls are representative for normal American newborns.

That the early fetal kidney can and does function now is well established, though the evidence rests chiefly upon animal experimentation. The literature on this topic has been well reviewed by Needham.[115] Cameron and Chambers[31] have been able to furnish the first direct evidence that human embryonic proximal tubules of themselves are able to function. They studied a living human fetus immediately after delivery by Cesarian section, of age estimated at $3\frac{1}{2}$ months. They found that the cut ends of segments of the tubules of the embryo kidney healed over in tissue culture, and that certain dyes, if present in the surrounding medium, passed into and accumulated in the lumina of the proximal tubules to a conspicuously higher concentration than that of the dyes in the medium. The experiments with phenol red showed that the proximal tubular fluid of the human metanephros has a pH of approximately 7.

7. **Miscellaneous.** *Acetone.* Ketosis with acetonuria is more common in children than in adults, and carbohydrate impoverishment plays a rôle in its production.[77,158] The modern conception of the physiologic mechanisms underlying the development of ketosis have been succinctly stated by Mirsky and Nelson[111] in their recent study on ketosis in children: "It has been demonstrated that the liver is the main site of the formation of ketone bodies; that any phenomenon which induces a depletion of the glycogen reserve in the liver will produce ketonemia; that the administration of adequate amounts of exogenous sugars can inhibit the formation of ketone bodies in diabetic and in non-diabetic organisms, even in the absence of insulin in the former; that the muscles of diabetic and of normal animals utilize ketone bodies with equal avidity; that there is a maximal rate at which ketone bodies are utilized by the muscles, and that excessive ketonemia will occur only when the rate of production exceeds that of utilization; that carbohydrate metabolism does not affect the rate at which ketone bodies are burned in the muscles, and that so long as the organism can maintain an adequate store or reserve of glycogen in the liver the rate of fat metabolism, and therefore the rate of formation of ketone bodies, cannot become sufficiently increased to cause an excessive ketonemia. Accordingly, it may now be stated that fats do not 'burn in the flames of carbohydrate' but 'the flames of carbohydrate inhibit those of fat'."

Thus, any phenomenon such as high body temperature which increases the metabolic need of the muscles for carbohydrate or which decreases the availability of carbohydrate for storage in the liver (*e. g.*, vomiting) will favor the development of ketonemia. It is wise, therefore, to give frequent meals and feed sugar-containing substances, at night as well as during the day, if necessary, whenever a child becomes ill with any infection or metabolic disturbance. This undue administration of carbohydrate will

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counteract the heightened susceptibility to ketosis of the sick child and help to prevent the development of acidosis.

Experimentally, Mirsky and Nelson found that phlorhizin glycosuria with a loss of 15 to 20 gm. of sugar from the normal child, or of a lesser amount from the diabetic child, resulted in hypoglycemia and ketonemia secondary to glycogen impoverishment of the liver. The younger the child, the smaller the reserve of glycogen in the liver, relatively speaking; this explains the greater susceptibility of younger children to ketonemia.

Amylase. That the amylase content of urine and blood becomes elevated during mumps is well established[47,60,93,113] High values may be found also in pancreatic diseases such as acute pancreatitis and obstruction of the common duct by stone, but such disorders enter pediatric differential diagnosis but rarely. The source of the excess of enzyme is presumably the affected glands—pancreas, parotids, etc. Urinary amylase may be present after the 2nd day of mumps, according to Dunlop,[47] who studied 60 cases. Since the titer in his patients was comparable with that of acute pancreatitis, he wondered whether pancreatitis occurred more frequently in mumps than is commonly supposed. He made it a rule to keep patients with mumps in isolation until the urinary amylase had returned to normal, which was often some days after parotid swelling had subsided. The determination of diastase in blood or urine can be helpful in distinguishing other localized infections of the neck, such as cervical adenopathy, from mumps.

Calcium. Excessive urinary calcium excretion can be detected by the simple test introduced by Barney and Sulkowitch[13] in 1937. When acidified urine is shaken with an equal amount of buffered oxalate solution of stated strength, an immediate dense cloud of calcium oxalate indicates a high concentration of calcium, whereas the absence of any precipitate almost always rules out excessive parathyroid activity. At the time of the test the diet must be free from milk, cheese and acidifying agents, since these can cause temporary increases in calcium excretion.

Albright[5] recommended the test for control of the dihydrotachysterol treatment of hyperparathyroidism. With patients on a high calcium diet the dose of dihydrotachysterol should be so regulated that the urine will not display a heavy cloud; in this way the serum calcium can be kept at a safe, slightly subnormal level.

The possible value of this test in detecting abnormal calcium metabolism in children was explored by Linder and Latsky[95] in a series of 114 children aged 9 to 15 years. They found no correlation between the mean serum calcium levels and the urinary reactions. A tendency was noted for the malnourished children with a serum calcium below 8.5 mg. per 100 ml. to give a negative test in specimens collected after breakfast. There were so many exceptions that they were forced to conclude that the Sulkowitch test for urinary calcium has only a very limited use in a nutrition survey. Linder and Latsky noted, as Barney and Sulkowitch, and Albright had done, that if several cups of water were given to children arriving with a "thick" test, the urine passed subsequently would be "clear." Reversely, the giving of milk caused "clear" urine to become "thick."

Obviously any test whose responses are so dependent upon the drinking of milk, which is a staple during the early years of life, and upon fluid intake, has scanty application to the field of pediatrics. Nevertheless it has proved helpful as a guide to therapy in hyperparathyroidism, both the primary variety and that associated with renal insufficiency.

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Chlorides. Expressed as sodium chloride, the daily output of urine chlorides in the healthy child is about 3 to 10 gm., being roughly proportional to age. The excretion reflects the intake in the diet. Excessive perspiration, diarrhea, pneumonia, nephritis and some other disease states will cause a urinary decrease. With the usual attack of pneumonia the urinary chloride drops to exaggerated low levels just prior to the crisis, reaches the lowest level at the time of the crisis, and then 1 to 3 days later rises abruptly to supernormal levels for 24 to 48 hours followed by prompt return to normal.[72,147,160] Antopol and Churg[9] followed 17 patients with pneumococcus pneumonia treated with sulfapyridine. The urinary chlorides began to rise on the 6th to 14th day of illness, the 3rd to 7th day after initiation of sulfapyridine therapy. Thus the chloride rise took place from 2 to 6 days, in a majority 4 to 5 days, following the crisis. Of the 17 cases, 9 were children from 9 months to six years. In 5 patients with sulfathiazole-treated pneumonia, Oshlag and Eil[117] noted similarly that clinical defervescence occurred several days ahead of the sudden reappearance of chloride in the urine.

Sherman and Corbin[137] using a simple qualitative test, described their experiences with the urines from approximately 300 children in 2 Chicago hospitals. Of these, 123 had greatly reduced or nearly absent urinary chlorides. In this latter group 82 (67%), had pneumonia and 19 (15%), had upper respiratory infections, leaving a miscellaneous collection of 22 (18%), with varied conditions; namely, 5 with prematurity, 4 prodromal measles, 2 peritonitis, 2 pneumonic and 1 influenzal meningitis, 2 nephritis, 2 eczema and 1 each of gastro-enteritis, sickle cell anemia, and acute appendicitis. They accounted for the decreased chlorides in the miscellaneous group on the basis of insufficient intake by the prematures and dehydration, edema, diarrhea or vomiting in most of the others.

Cystine. The metabolic fault in cystinuria appears to be an inability to oxidize the normal proportion of endogenous sulfur to sulfate, and to excrete it as such. Instead, unusually large quantities of cystine enter the urine, and tend, on standing, to settle out as characteristic flat hexagonal crystals. The level of cystine excretion in the cystinuric is fairly constant, but it can be raised by a high protein diet, independent of the sulfur content of the particular proteins eaten.[109] Brand, Harris and Biloon[25] have described a qualitative cyanide-nitroprusside test which makes possible quick screening of urine for cystine. If this reaction is positive, the more difficult Sullivan[146] naphthoquinone should be done to confirm the finding.

The familial incidence of cystinuria is now well established. Lewis[92] encountered 4 frank cases and 14 likely ones in 11,000 urines of healthy young male and female college students. In adults, the condition is typically benign and usually not suspected, but occasionally such subjects develop symptoms from cysteine calculi. The urologists recognize that the danger of calculus formation is always present, and have found that an alkaline ash diet low in protein is helpful in preventing stones from forming. Andrews and Brooks[8] state that there are no cases on record in which a cystinuric subject has ever formed a calculus of any other composition than practically pure cystine.

In children, cystinuria may provoke more violent disturbances than those above described. Cases have been reported by Abderhalden,[2] Lignac[94] (3 cases), Fanconi,[58] and Beumer and Wepler,[19] of young children who died with symptoms of nutritional failure, and at postmortem had cystine crystals in many organs by both microscopic and chemical examination. These autopsy findings suggest that enzymatic inability to metab-

olize essential cystine was the mechanism behind their failure of normal growth and nutrition. Three of these 6 cases had proteinuria and renal glycosuria, attributed to malfunction of the infiltrated kidney.

Indican. Several studies on the excretion of this substance have been reported by Sharlit.[136] Indole, which is formed solely in the intestines from tryptophane, is detoxified by the liver through oxidation to indoxyl and conjugation with sulfuric acid to form potassium indoxyl sulfate, or indican. The excretion of large amounts of indican in the urine may be accepted as evidence of inordinate putrefaction of protein in the intestine. Sharlit[136b] collected single chance specimens of urine from each of 35 infants between 2 months and 2 years of age, each of whom had an eruption—usually some form of eczema. The quantities ranged from faint trace to 87 mg. per liter—values which were probably in excess of normal amounts, though distinctly less than might be expected from protein putrefaction due to intestinal stasis of any marked degree. Sharlit[136a] found also that newborns aged 3 to 19 days excrete appreciable amounts, though he made no attempt to correlate the quantities with the exact daily age, laxation rate or kind of milk being fed.

Phenylpyruvic Oligophrenia. This is a rare metabolic error, congenital and hereditary, characterized by mental deficiency, neurologic disturbances and phenylpyruvic acid in the urine. Dann, Marples, and Levine[37] subjected a 25 month old boy with this disease to extensive metabolic tests. They found his urinary content of this substance to vary from 0.45 to 1.03 gm. per 24 hours. Appreciable amounts of phenyllactic acid (0.20 to 0.55 gm.) and of phenylalanine (0.21 to 0.32 gm.) were also being excreted. On the basis of these and other experimental findings they concluded that the defect in this disease is an inability to properly metabolize phenylaline. Ascorbic acid in large doses did not induce improvement. For accuracy in diagnosis, the authors recommend a urine examination for phenylpyruvic acid of every infant and child suspected of being mentally retarded. The test is easy to perform. If phenylpyruvic acid is present, acidified urine, when 5% ferric chloride solution is added, assumes a transient characteristic green color.

17-Keto Steroids. The urinary excretion of 17-keto steroids in children has been reported on by Talbot and associates.[149] The output of these substances was very low from birth to approximately 10 years, rising gradually with older children as they approached 18 years of age, with no significant difference between boys and girls. During the period from 8 to 18 years, the average output rose from less than 1 mg. to approximately 9 mg. per day. Because values approximating 0 mg. may be considered normal for children under 10 years of age, detection of abnormally low excretion in children under that age is not possible. However, children who have reached their 12th birthday should excrete at least 1 mg. of 17-keto steroids daily. A tendency toward moderate elevation in output of 17-keto steroids was observed in apparently "normal" children with physiologic sexual precocity and in abnormally overweight children whose development tended to be accelerated. Abnormally low values for excretion were obtained for children over 12 years old whose growth and development were retarded. The excretion of 17-keto steroids of patients with mongolism was not consistently abnormal.

Tyrosine and Phenylalanine. A spontaneous defect in the metabolism of tyrosine and phenylalanine was discovered by Levine, Marples and Gordon[91] in premature infants being raised on cow's milk. Full-term infants on similar diets did not excrete these aromatic amino acids. Chrom-

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ogens were encountered, while studying the urinary excretion of creatinine by prematures, which gave the Jaffe reaction but none of the other characteristic tests for creatinine. By careful analysis these substances were found to be *l*-p-hydroxyphenyllactic and p-hydroxyphenylpyruvic acids. When these amino acids were fed in pure form their urinary excretion became augmented. When the feeding mixture contained 5 gm. or more of cow's milk protein per kg. body weight per day, these abnormal substances were present in quantities of 300 to 500 mg. of tyrosine equivalent per kg. body weight per 24 hours. On the other hand, with breast milk, which contains much less protein, or with a cow's milk mixture of greatly reduced protein content, the daily excretion fell to below 10 mg. The authors were able to show that this behavior was brought out most fully when there was no vitamin C in the diet. Conversely, the administration of *l*-ascorbic acid completely eradicated the defect without necessarily raising the plasma ascorbic acid level. The administration of *d*-isoascorbic acid had a less definite partial effect. None of the other known vitamins produced any improvement. The reversibility of this metabolic aberration differentiates it from such hereditary anomalies as alkaptonuria and phenylpyruvic oligophrenia which are not correctible with vitamin C.

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GYNECOLOGY AND OBSTETRICS

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CANCER OF THE CERVIX

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The problem of cancer is far from solved, but each year one or two bits of information are unearthed which may be small pieces in the gigantic

jig-saw puzzle. While the present status of the situation is not too encouraging, there can be no doubt that, on the whole, our knowledge of the subject and the results of treatment are improving. Until we know the cause of cancer, treatment cannot be fully efficient, and much praise should be given to the many investigators who are working on this phase of the subject. The widespread use of estrogenic substances in various gynecologic disorders has prompted an editorial comment[7] on the work of Gemmell and Jeffcoate,[8] who have observed the appearance of carcinoma of the cervix in 3 patients among 43 who were treated with estrogens for kraurosis vulvæ and senile vaginitis. The occurrence of these 3 cases cannot prove that carcinoma cervicis may be caused by estrogens, but they point out some practical lessons: (1) Every patient of menopausal or postmenopausal age, presenting symptoms of discharge, should be subjected to the most careful investigation to exclude carcinoma of the uterus, even when some lesion such as senile vaginitis appears to be the obvious cause. (2) Estrogens should be administered with caution if the patient has a lacerated or infected cervix or any other precancerous lesion. (3) Estrogens should probably not be administered to patients with a strong family history of malignant disease.

Diagnosis. In order to obtain the best results in the management of cancer of the cervix, it is essential to diagnose the disease in its early stage.

The iodine test which Schiller[22] has popularized, will indicate suspicious areas in the cervix which should be subjected to biopsy. This test is based on the fact that the upper layers of the normal epithelium of the portio and the vagina contain rich masses of glycogen which disappear when the epithelium becomes cornified or changed by cancer. In the normal living tissue, the glycogen of the upper layers of cells is stained, in a few seconds, a deep mahogany brown by iodine in watery solution (Lugol's solution). A superficial area of early cancer, being devoid of glycogen, does not receive the stain and stands out startlingly white or pink against the deeply colored background of normal tissue. While the test is simple, it is not without its limitations. It appears to be completely reliable when it is clinically negative, that is to say, when all the tissues take the normal stain, therefore the test is specific in the *absence* of cancer, but there are several conditions that obscure the test, and with these the examiner should be thoroughly familiar. The stain does not take on glandular epithelium like that of the endocervix, hence an eversion would appear pink and an adenocarcinoma, which fortunately is rare, would not stain. Ulcerations and erosions have no epithelial covering of the squamous type, and hence do not stain. In areas of chronic cervicitis, the epithelium is often deficient in glycogen, taking a very light brown stain which blends with surrounding deeply staining tissue, instead of being sharply defined from it as in cases of cancer. It is also important to remember that the normal stain is prevented or obscured by a slight trauma such as that from tenacula or scrubbing with gauze. This is caused by the rubbing off of the upper layers of epithelium which contain the glycogen. The cervix and vagina of the hypoplastic and atrophic individual, stains lighter than the normal, but during pregnancy the stain is especially deep. Pus stains black, but living granulations do not take the stain, while mucus, blood and douche water obscure the reaction. Hyperkeratosis prevents the stain as in leukoplakia, lues, and exposed areas in prolapse. The test is of value only in cervical cancer and is not adapted to other superficial cancers, such as those of the vulva and skin in other parts of the body. This is due to the fact that the epidermis

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of the portio and vagina is not cornified and that the upper layers of cells contain a special chemical type of glycogen. Schiller states that it is a mistake to carry out the test in suspicious cases only. We see carcinomas in women who never had leukorrhea, never had a discharge, in women with perfectly smooth cervices and portios. He has discovered a number of early carcinomas in young women who came for backache, cystitis, or some other unrelated complaint. He believes that if we could examine all women once or twice a year, by the iodine test, then we would succeed in getting all carcinomas in the initial phase and all would have a definite possibility of cure.

Novak[19] states, however, that both this test and the use of the colposcope are of rather limited value. Neither procedure is of the kind which can be expected to achieve adoption by the general profession, nor is this desirable. Considerable experience is necessary for proper interpretation with either method, and neither is of much value unless combined with biopsy and pathologic diagnosis, so that it is quite certain that the general practitioner will wish to transfer this responsibility to the specialist who is trained in such matters. Colposcopy, moreover, is a time-consuming procedure. The chief value of the Schiller test, even to the expert gynecologist, is to indicate the proper points for biopsy, though in the great majority of these cases the suspicious areas are apparent enough, sometimes pathetically so. The same statement may be made concerning the colposcope, so far as actual cancer is concerned. Novak does not believe that a good gynecologist who examines the cervix very carefully in a very good light, will overlook many cancers that the colposcope would reveal. Moreover, this procedure as well as the Schiller test, is obviously intended chiefly for the detection of the earliest cases, those in which there has been no bleeding, for the occurrence of the latter presupposes that ulceration has already begun. To pick up these very early cases, the colposcope would have to be used practically as a routine, which is almost out of the question in most clinics. In cases in which symptoms have already developed there is rarely any difficulty in finding the suspicious area with the naked eye. In the opinion of Martzloff,[14] the iodine test is not specific for cancer or for areas of so-called probably beginning cancer. According to his experience, the overwhelming majority of unstained areas, including areas of leukoplakia, show no histologic evidence suggestive of probably beginning cancer. Small epithelial gland plugs, vermilion areas, a proportion of superficially situated nabothian follicle cysts, area of epithelial loss, either when superficial or, if complete, apparently when fibrin covers the base of the ulcer, epithelium involved in an underlying inflammatory process and particles of adherent inspissated secretion, together with other unexplained areas, fail to stain with the iodine. It follows that, if areas that do not stain with iodine are not interpreted with due reserve, they lead to endless confusion and alarm for the physician and unnecessary biopsy, cervical tinkering, and hysteria for the patient. He has not discovered a histologically proved area of probably beginning cancer with the iodine test, nor has the test proved to be of any more assistance than careful inspection with the unaided eye.

Since most authorities agree that the absolute diagnosis of cervical cancer must depend on the microscopic examination, usually of a biopsy specimen, Henriksen[10] cautions that the amount of tissue for study must be sufficient to include not only the suspected area, but also some of the apparently normal tissue. For satisfactory interpretation of the histologic picture, an aggregate view of the changes must be obtained. Diag-

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nosis based on the individual cellular changes is hazardous, especially when the tissue is scant in amount. One section from the area in doubt frequently misses the suspected process, while serial sections of the specimen will not uncommonly reveal the real nature of the lesion. The dangers of infection, dissemination or stimulation of the tumor growth, and hemorrhages, are apparently not as dangerous as they were once considered by many. In spite of any possible risks, the data obtained more than counterbalance them. That stimulation of the tumor growth occurs is not supported by the evidence now available; there is no proof that the growth is accelerated, and animal experiments show no change in the growth rate following trauma. Three days after taking a biopsy from a normal cervix, the wound is usually completely healed. Hemorrhage, except in advanced cases, rarely occurs, and at most amounts to only a slight venous ooze. An important factor in taking the biopsy is immediate fixation, for it has been shown that the alkaline secretions of the cervix bring about a definite fading of the nuclear particles, and thus the resultant microscopic picture is hazy. Immediate freezing and staining is the ideal method; but when permanent serial sections are desired from a small bit of tissue, this procedure is difficult and undependable except in the hands of an expert. Henriksen states that the divergence of opinion as to the diagnosis in very early carcinoma of the cervix is disheartening, many still seem to cling to the older concepts of cellular confusion so characteristic of the late stages. At the other extreme are those who scent malignancy wherever there is a departure from the accepted normal of cellular activity. In order to appreciate fully the pathology of the cervix, one must be especially equipped to diagnose the very early case. To attain this knowledge, one must possess a familiarity with all the various cellular changes, checked by careful follow-up studies in each case. Merely to call the changes "suspicious" or "doubtfully malignant" is of little aid to the clinician, who, if possible, wishes to be informed that the lesion is either benign or malignant. If the pathologist cannot decide either way, the responsibility reverts to the clinician; though when such doubt exists, the wise plan is often to defer active treatment until the question can be definitely settled, for such a slight delay will rarely endanger the patient.

Statistics show that in the United States 10% of patients with cancer of the cervix are nulliparous. In the Department of Gynecology (Univ. of Pa.) this percentage is about the same, as Tompkins[26] reports 53 cases in nulliparæ in a series of 505 patients treated. In a detailed tabulation of various phases of the disease, including race, age, extent when diagnosed, histologic type, treatment, and results, he found that this disease in the nulliparous differs in no respect from cancer in parous women. It is of passing interest to note that all of the cases in nulliparous patients were in white women and none were Jewish. In a clinical study of 940 cases of cancer of the cervix in Johns Hopkins Hospital, Henriksen[11] found that the average age was 46.1 years, while two-thirds of the cases occurred before the age of 50 years. Over 10% had never been pregnant. Bleeding from the vagina is the most frequent symptom, averaging 6 months before applying for treatment. Postcoital spotting occurred in less than 5%. Involvement of the urinary tract was present in 50% of the cases, with nocturia the most frequent complaint. Pregnancy has some influence on the growth of the tumor, while cervical laceration is a cardinal factor in producing chronic irritation. The average Hb. content was 75%, which is not much below average for normal women. Loss

of weight has no diagnostic value, as one-half of the patients had no loss. Pain rarely appears before parametrial invasion, unless due to associated pelvic lesions. In this series there were 22 cases in the cervical stump following subtotal hysterectomy, with an average lapse of 5 years. He assumes the growth to have been preëxistent to operation if it occurs within 2 years. The incidence of cancer of the stump in this series is less than 0.2%. Rectal invasion is rare, except in advanced cases. That cancer of the cervix is rare in adolescence is confirmed by the report of Bowing and McCullough,[3] who point out that among 3000 patients with malignant neoplasms of the uterine cervix referred to the Mayo Clinic, only 1 instance of cancer in a patient less than 20 years of age was found. This occurred in a white girl of 13. The case emphasizes the need of making a careful manual and visual examination as well as microscopic and pathologic examination of any tissue which may be at all suspicious. They believe that, because of the rarity of the disease among patients 20 or less years of age, and of the difficulties encountered in making the diagnosis and the emphasis placed on the so-called cancer age, the diagnosis of cancer among young women is frequently confused or missed entirely. A search of the literature since 1862 revealed 25 cases of carcinoma of the uterine cervix in girls 20 years of age or younger.

Since leukoplakia is often considered to be a precancerous lesion, it is interesting to note that Schiller[23] states there is no causal relationship between para- or hyperkeratosis and carcinoma of the portio. From extensive material he could not find even 1 case of carcinoma that developed from a true keratosis. Cases with prolapse are excluded in this study; at best they disprove any relationship between carcinoma and cornification. In other parts of the body—mouth, lips, for example—cornification plays an important r$le in the etiology. These areas of leukoplakia do not warrant radical treatment, such as amputation of the portio advocated by some authors as a prophylaxis against possible malignancy. He found that these areas of leukoplakia remain for years without undergoing any changes. Malignant degeneration after 10 or 20 years cannot be excluded, but his observations point against it. If the histologic diagnosis is definitely established, a periodic examination is sufficient. Radical therapy is not justified. These areas of leukoplakia are to be grouped with the benign hyperkeratosis of the skin rather than with the leukoplakic areas of the mucosa of the mouth or larynx. As a means of making an early diagnosis in uterine cancer with a minimum of expense and annoyance to the patient, Papanicolaou and Traut[20] have advocated the study of vaginal smears. Cervical malignancy, in their experience, is revealed in vaginal smears by the appearance of characteristic cells. These are derived from the superficial layers of the tumor which undergo continual desquamation. These cells show great variety of form and size, much greater than that seen in sections of the tumor. Their distinctive features lie in their structural abnormalities. They do not fall into the categories of any of the cell types found in the vaginal fluid of normal women or of women having benign tumors or other pathologic lesions of the uterus. The most characteristic feature of the abnormal cells is the atypical form and structure of their nuclei. These often are very large, far surpassing normal size. The chromatin frequently shows a characteristic distribution in the form of conspicuous granules and of one or more small nucleoli. The cytoplasm also shows abnormal changes. It is often dense and hyperchromatic, particularly in the cells of the basal type. Such cells may appear either singly or in compact dark-staining

clusters. Their form and size vary greatly. Some of the basal cells assume elongate, spindle-like, triangular or ameboid forms. Basal cornified cells are not uncommon. Vacuolization of the cytoplasm is a characteristic feature. The vacuoles may be empty, or they may contain leukocytes, erythrocytes, cellular débris, or some pink-staining fluid. Sometimes the vacuoles occupy one side of the cell, while the dense cytoplasm and the nucleus are concentrated on the other side. A commonly found, very characteristic cell type is an extremely elongated one resembling a smooth muscle fiber. Long fibrous cells of this type are modified epithelial cells, and appear either isolated or in groups. Another deformed cell type which is often seen, is one having the form of a tadpole, with a spherical head containing the nucleus and a tail-like prolongation. The bulging of the heavier part which contains the nucleus is sometimes placed more centrally, causing a narrowing of the cell at both ends. Other cells attain very large sizes and acquire the most unusual forms. These "aberrant" cell types are numerous only in advanced cases of malignancy. They are relatively rare in the early stages of the disease, and a thorough search of several slides is often necessary before their presence can be established. For this reason, a negative diagnosis should always be made with extreme caution. Considering that, even in the advanced cases, the number of cells derived from the tumor forms only a small part of the total number of desquamated cells present within the vagina, it is natural to find the normal epithelial cells always in the majority. Blood elements are quite conspicuous in the vaginal smear of cervical malignancy. Erythrocytes are generally found in large numbers. Many show degeneration and have lost their hemoglobin. Fibrination is very pronounced. The complete absence of blood is so rare, even in the early stages, that it may be considered in favor of a negative diagnosis. The leukocytes are, as a rule, very numerous, more particularly in the advanced cases. After trying this method at the Massachusetts General Hospital, Meigs[15] has been impressed with its accuracy, and believes it should be widely used. He states that a negative diagnosis should not be accepted as final in any patient with a suggestive history or examination. In any suspicious case, a negative smear must be checked by many more slides and by examination of biopsy material. A positive diagnosis does not mean that radical surgery or radiation should be undertaken, but indicates that confirmatory biopsies of the cervix or endometrium should be performed. Any patient with a positive vaginal smear who is without clinical evidence of cancer should be followed closely by repeated examinations and smears. The ease with which material for diagnosis can be obtained by this method makes the technique adaptable to office and out-patient department practice. However, since the recognition of cancer cells in the vaginal smear requires an experienced knowledge of cytology, it is suggested that there should be in every hospital a service for the interpretation of smears. It is his opinion that no longer can the vaginal smear be omitted from the routine examination of any female patient who is in the cancer age group.

Prognosis. Biopsy material from 728 cases of carcinoma of the cervix has been examined by Chambers,[4] and 500 cases have been histologically graded based on the extent of differentiation and degree of cell activity and also on the general architecture of the growth. The results of treatment have been recorded, with special reference to the local area of the cancer at the primary site in relation to the histologic type. The highest percentage of local cures has been obtained in the transitional type of squamous cancer (73.8%) and in the adenocarcinomata (72.9%), but

none of the histologic grades show a difference of more than 15% in either local cure or in the number of 3-year survivors. There is no evidence that adenocarcinomata are insensitive to irradiation. Following a careful analysis of the survival rates of patients following irradiation, Meigs and Jaffe[17] have found that the first 2 years are the serious years for patients with cancer of the cervix, for in the 3rd and 4th years, respectively, less than 9% of the total number of cases, not including the survivors, died. In the 5th year not over 5% died, and in the 6th, 7th, and 8th years not over 2%. Thus it is evident from these various charts that end-results in a series of cases of cancer of the cervix treated by radium or radium and Roentgen ray can be predicted by subtracting 10% of the total number for the 3rd year, 10% for the 4th year, and 5% for the 5th year, and results up to the 8th year by subtracting 2% for each of the next 3 years. This should be of great value. Thus, if at the end of the 2nd year in a group of 100 patients, 54% are alive, 10% may be subtracted for each of the next 2 years, leaving 34% and for the 5th year 5%, leaving 29% of predicted 5-year survivors. Thus, final results will be within a 5% error. Such mathematical maneuvers are of enormous value, for the therapeutist can satisfy himself of his expected results after a follow-up of 2 years, and certainly after a follow-up of 3 years. It is obvious that most of the deaths occur in the first 2 years, and most patients who have no obvious disease at the end of 2 years have a good chance for recovery. They state that it is only necessary to follow our cases for 3 years following treatment, and then by deducting 15% the 5-year end-results can be predicted. Therefore, it is unnecessary to wait for 5 years following treatment before reporting a group of cases or to change a method of treatment. For those patients who have survived the 5-year period, the report of Kimbrough and Tompkins[13] based upon 304 patients treated at the Hosp. of the Univ. of Pa. is helpful. They found that 23.3% of the patients survived 5 or more years, and 18.7 of the original group lived more than 10 years after treatment. In other words, four-fifths of those who survived 5 years lived at least 10 years after treatment. Based on her observations of over 900 cases of cancer of the cervix at the Marie Curie Hospital in London, Goldschneider[9] states that the occurrence of pyrexia in the course of radium treatment is an unfavorable development and usually indicates an increased immediate mortality as well as a reduction in the number of 5-year cures.

Radiotherapy. For many years irradiation has been advocated by most gynecologists as the safest and best method of treatment, but lately there has been a trend back toward operative treatment. In order to compare these 2 types of treatment, Jones and Jones[12] have reviewed a selected group of 36 cases of early carcinomas of the cervix treated with panhysterectomy and compared the results with 704 unselected cases in all stages, treated with radiation. Although irradiation has been demonstrated by numerous observers over a period of years to be more satisfactory than panhysterectomy for the average case of cervix carcinoma, it is the opinion of many gynecologists and general surgeons that operation is a satisfactory method of therapy for very early cases. That panhysterectomy is commonly selected in such cases is indicated by the fact that, in their experience, for every 10 patients with primary carcinoma of the cervix there is 1 admitted for treatment of a recurrence after operation. During the years 1927 to 1937, 36 patients with early carcinoma of the cervix were carefully selected for operation at the Johns Hopkins Hospital. In spite of this careful selection, a 5-year cure rate of only 41% was

obtained. This does not compare well with the cure rate of 57% obtained by irradiation with less favorable material. It has, therefore, been concluded that as a practical therapeutic procedure for early carcinoma of the cervix, panhysterectomy is an unsatisfactory method of therapy. Irradiation is the treatment of choice.

While the present study strongly suggests that operation is not the method of choice in early Stage 1 cases, especially in the transitional and spindle cell groups, it does not at all indicate that the "accidental" and preinvasive lesions should not be operated on. In the 36 cases of the operative series herein reported, 5 belong to this group. All these patients are living except 1, who died of postoperative shock. With the information at hand, the question of operation or irradiation cannot be definitely decided for this group. In a more general consideration of the selection of type of therapy for these early cases of carcinoma of the cervix, it is worth noting that, although the lesion in several instances was thought to be of the earliest, there was found on examination of the gross operative specimen, a large intracervical nodule of cancer. For this reason, and because of the experience considered in this paper with slightly more advanced squamous cell lesions, they feel that irradiation will prove more satisfactory for the entire squamous cell group, including the "accidentally" discovered and preinvasive lesions. If radium is selected as the method of treatment, full dosage should be employed, because early lesions of the cervix may be more extensive than clinical examination can indicate.

While the application of radium under ordinary conditions is a comparatively simple procedure, there are many complications which may occur. In presenting some of these, Cutler[6] mentions the condition which renders it difficult and sometimes impossible to introduce radium safely into the cervical canal, namely, occlusion of the canal by the growth. The danger of perforation in an effort to locate the cervical canal under these circumstances is well known. Experience has demonstrated the importance of avoiding this danger. This can be accomplished by initiating the treatment with external and vaginal radiation. The regression of the lesion following these procedures, with rare exceptions, results in a disappearance of the occlusion so that the cervical canal can be located without undue trauma and with no danger of perforation.

Pyometra may be divided into 3 groups: (1) Early pyometra due to occlusion of the cervical canal and appearing toward the end or within several weeks after radiation. This complication should always be considered and recognized as early as possible. Dilatation of the cervical canal and drainage frequently terminates this complication. (2) Late pyometra occurs from 1 to several years after treatment. The condition has to be differentiated from recurrence. The treatment is the same as for early pyometra. Occurring long after treatment, the diagnosis is more likely to be missed. (3) Late infectious parametritis, a complication that arises usually 1 to 3 years after radiation treatment. It may be due to a reactivation of an old latent infection or to a new infection which becomes localized in tissues of a lowered resistance. This inflammatory complication must be differentiated from recurrent cancerous disease.

Infection during the process of irradiation is by far the most important complication associated with the radiotherapy of the cancer of the cervix, the 2% mortality charged against this procedure being due almost exclusively to the activation of hemolytic streptococci by the radiation. In an effort to determine the virulence of the microörganisms, Ruge devised

a clinical test which has been amplified by Philipp. The Ruge-Philipp test determines the ability of the patient's microörganisms to grow in a medium containing the patient's own blood. If the bacteria grow and multiply they are considered virulent. If they fail to grow or if they diminish in number they are considered of uncertain virulence. With this classification it was found that radiation treatment in the presence of avirulent streptococci resulted in 1 death (2%). One patient developed severe complications and 48 had a smooth convalescence. Of 22 carriers of virulent streptococci, 5 (19%) died, 8 showed severe complications, and 13 showed a smooth convalescence. Many procedures have been advocated to combat this complication. Antiseptic douches, hypertonic salt solutions, copper salts, vaccines, autovaccination and antistreptococcus serum have been recommended. Since the introduction of sulfanilamide and its derivatives, several reports have appeared in the literature indicating their value in the treatment of these infections.

Intestinal injuries resulting from irradiation have been studied by Aldridge,[1] who states that they usually manifest themselves with the onset of intestinal symptoms, such as abdominal pain, frequent bowel movements, rectal tenesmus, and passage of varying amounts of blood and mucus by rectum. In some cases, the initial symptoms are those of intestinal obstruction, that is, abdominal pain, anorexia, nausea, vomiting, and obstipation or obstipation alternating with diarrhea. When these symptoms appear, they may be due to a temporary partial intestinal obstruction caused by hyperemia, edema, and spasm of the bowel at the site of an intestinal ulcer, or to a true organic stricture resulting from the formation and contraction of scar tissue as Nature attempts to heal the injured bowel. Symptoms of an intestinal injury may develop at any time from immediately following irradiation therapy to within several months or years later. Acute proctosigmoiditis is the mildest form of intestinal injury observed as a result of the secondary effects of irradiation therapy for uterine carcinoma. Characteristic intestinal symptoms appearing during the course of the treatment or soon after its completion give the first warning of the presence of such an injury. The symptoms include abdominal pain, diarrhea, rectal tenesmus and the passage of small amounts of blood and mucus by rectum. Examination will reveal a typical localized inflammatory process involving the anterior wall of the rectum and distal end of the sigmoid at about the level of the cervix. The mucous membrane over the area is soft to palpation, intensely hyperemic in appearance or edematous with considerable mucous secretion over its surface. Trauma of the palpating finger or passage of a proctoscope readily induces slight bleeding. With a bland diet and suitable palliative treatment, these mild injuries heal spontaneously and symptoms disappear soon after termination of irradiation therapy, leaving no evidence of damage to the mucosa or wall of the intestine. When injury to the bowel is more severe than that which causes an acute proctitis, ulceration of the intestine usually occurs. Although ulcerative lesions have been observed on both the rectum and sigmoid, the usual location for their development is on the anterior wall of the bowel at about the level of the cervix or at about 8 to 10 cm. from the anus. In a small percentage of these cases, perforation of the bowel occurs into the peritoneal cavity, causing peritonitis; into the vagina, producing rectovaginal fistulas; or into the perirectal tissues, giving rise to ischiorectal abscesses requiring incision and drainage. Ulcerative lesions make their appearance at any time from soon after termination of irradiation therapy to within several weeks or months later.

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They tend to heal slowly with separation of sloughs from their bases and inward growth of the surrounding healthy intestinal mucosa. Injuries resulting in acute proctitis and ulcerative lesions appear to be confined essentially to the mucosa and wall of the intestine itself and have been referred to as "intrinsic lesions." There are a few other cases in which the primary injury appears to have involved the perirectal tissues. The characteristic tissue reaction following such injuries is the formation of a diffuse mass of fibrous tissue involving all the pelvic structures below the uterocervical junction and extending upward and backward to the second or third sacral vertebra. This type of tissue reaction to irradiation referred to as an "extrinsic lesion" produces a pelvic condition which is difficult to differentiate from the so-called "frozen pelvis" caused by massive invasion of all pelvic structures by malignancy. It may be associated with an ulcerative lesion of the bowel. As healing of this type of injury progresses, the lower bowel is likely to be distorted by contraction of the fibrous tissue and by external pressure causing intestinal obstruction. That this condition is not a rare one is shown by the report from the Mayo Clinic by Randall and Buie,[21] who present data on 88 cases in which significant symptoms led to proctoscopic examination and a diagnosis of factitial changes in the rectum following radiation therapy. These symptoms, in order of frequency, were most commonly bleeding from the rectum, mucous discharge, and constipation. Other complaints that were made less frequently were of abdominal cramps, decrease in the size of the stool, and tenesmus. The average time that elapsed between the initial course of treatment and the appearance of symptoms was 10 months. Ten patients complained of various rectal symptoms that commenced immediately after treatment, and 3 patients noted the first symptom, bleeding from the rectum, 38, 40 and 48 months, respectively, after the initial treatment. Except in those few cases in which ulceration is sufficient to lead to formation of fistula, or in the occasional case wherein actual involvement of the rectovaginal septum by the malignant process is responsible for breakdown of the tissues, healing will take place, providing the patient survives the malignancy for a sufficient time. Healing is accompanied by scarring, occasionally some reduction in the size of the lumen of the rectum and by telangiectasis which usually produces bleeding from the rectum. Usually the patients can be taught proper care of the rectum. It should be explained to them that time is one of the most necessary factors to be considered, and that treatment usually is prolonged. The patient should take a warm, cleansing enema after each defecation in order to keep the rectum as free from fecal matter as possible. She is then instructed to inject 2 fluidounces (60 cc.) of warm hamamelis water (witch hazel), to be retained until the next movement of the bowel. Often the injection of 2 fluidounces of warm olive or mineral oil before retiring is of benefit. A bland diet, reënforced with some substitutes to furnish bulk, such as are now available, allows a soft stool free from irritating particles. Caustic medicaments should not be applied.

Following his experiences with nearly 50 cases of rectal ulceration, or as he calls it "pseudo-carcinoma of the rectum" following cervical irradiation, Todd[25] states that colostomy is frequently necessary, especially if stenosis, hemorrhage or severe pain are prominent symptoms. In order to prevent the occurrence of rectal ulceration, he gives several suggestions which sound valuable. He states that in order to utilize to the full the possibility of obtaining distance protection from the rectum, all vaginal applications of radium should be made with the patient in the knee-chest

position. The lips of the cervix, or a portion of the growth, should be sutured over the intrauterine tube to ensure that it does not slip into the vagina, or alternatively, a special type of applicator devised to prevent this complication, should be used. A locking device for the vaginal applicators should be used in order to prevent slipping and approximation. Repeated skiagraphs should be made during treatment to ensure that the position of the applicators remains constant; if slipping occurs, it is recognized, and the radium can be removed before damage is done. In the presence of retroversion, the intrauterine dose should be reduced, or the distal needle omitted in subsequent applications. A special applicator should be used during Roentgen ray treatment to limit the amount of radiation delivered to the rectum. Routine blood counts during treatment will demonstrate any marked constitutional effect due to the radiation. A pronounced lymphopenia indicates the advisability of stopping treatment. Preliminary proctoscopy will show whether or not the rectal mucosa is normal before radiation. Should rectal symptoms occur during treatment, proctoscopy will show whether or not there is any excessive reaction, and will decide whether the continuance of treatment is safe.

Operative Treatment. As previously stated, there is a tendency toward the resumption of operative treatment in this country, but in Europe there have always been some gynecologists who favored the surgical operation in spite of the favorable results others were achieving with irradiation. In 1936, Bonney[2] did his 500th Wertheim operation during a period of 34 years. In the operation he removes nearly all of the vagina, the uterus, appendages, iliac and obturator glands, and as much of the parametrium as possible. In addition to marked extension of the growth, operation may be contraindicated on account of grave diseases of the heart, lungs or kidneys, severe diabetes or gross adiposity. In such cases he advocates radium. He does not use radium preoperatively nor Roentgen ray postoperatively. Of the 500 cases, 201 were well after 5 years, 193 recurred before 5 years, 36 were not followed or died of other diseases, and 70 died of operation. Thus the absolute cure is 40%, the relative salvage is 43% for 5-year statistics. About 65% of recurrences occurred within 2 years after operation. Recurrences were treated by irradiation, but uniformly without success. He considers recurrence after a Wertheim operation as practically incurable by any means. The operative mortality rate of 14% was largely due to shock. In about 40% of the cases the regional glands were involved, and in these the 5-year cure rate was only 23%, as opposed to the cases free from gland involvement and where the cure rate reached 58%. Similarly, the operative mortality was only 10% in the gland-free cases against 20% for the gland involved group. Vesical fistula occurred 8 times, 1 cured by operation, 1 closed spontaneously, 4 remained open until death and 2 operated with death. Ureteral fistula—8 cases, 3 closed spontaneously, 2 cured by grafting ureter to bladder, and 3 remained open until death. Ureter divided accidentally only once, but intentionally 12 times with implantations in the bladder, of whom 5 died of operation, 2 of recurrence, 2 are 10-year cures, 1 a 5-year cure and 1 died of coronary thrombosis years after the operation. He admits that radiation gives results as good as surgery with much less risk, and states that no surgeon should undertake the operation unless he has served an apprenticeship in it, as it is the most difficult of gynecologic operations.

In order to determine the status of therapy in cervical cancer in Central Europe, Mikulicz-Radecki[18] collected statistics from 11 important clinics, embracing cases treated between the years 1919 and 1926, only a few of

these statistics having been previously reported. The combined series totaled 5455 cases. Of these, 34.8% were operated upon and usually supplemented by postoperative irradiation. The remainder of the series was treated by irradiation alone, except for 5% which were hopelessly inoperable and were not treated at all. Of the entire series, 24.5% were cured, which is the best absolute cure rate thus far published in such a large series. One clinic (Stoeckel) reached the very high rate of 36.5% of absolute cures. It should be borne in mind that absolute cures represent the percentage of all patients seen and not merely the percentage of those treated. Of course, in this series, since all but 5% were treated, the absolute and relative cure rates would not be very different. Armed with such statistics he states that such "elective therapy," that is selecting the type of treatment for the individual patient is the best method of treatment. This means that from 20 to 40% of the patients should have the radical operation with the greatest possible removal of parametrial tissue. He believes that the radical operation is superior to the irradiation alone, but simple hysterectomy is a useless procedure. Abdominal and vaginal radical operation give comparable end-results, but the mortality of the vaginal operation is lower principally because of the less chance of infection as a complication. Any operative procedure, however, should be reserved for the good risk patient if the mortality is to be kept low. These patients should have Roentgen irradiation postoperatively, but in cases where satisfactory removal of the parametrium is doubtful, radium is applied in the parametrial and pararectal spaces. Preoperative irradiation is employed in cases in which it is hoped to bring them from the doubtful to the operable class, but as a routine treatment in all operable cases it only wastes valuable time, and its value as a preventive of postoperative infection has not been proven. All inoperable cases should be treated with intensive radium or Roentgen irradiation.

Crossen[5] states his views on the subject editorially by saying, in his book "Operative Gynecology," that he expects to retain a description of the radical operation because of its historical importance in the development of the effective treatment of this disease. However, as a method of choice in the handling of carcinoma of the cervix today, radical operation as opposed to irradiation is a back number, an obsolete method. He feels that it will probably take 10 years for this knowledge to permeate the profession and bring to the patients generally the benefits of a most effective treatment, especially if journals and books push the operation. Briefly stated, he believes that the successful care of a patient with carcinoma of the cervix is based upon an organized combination of expert services. The crucial point of attack is not in the uterus but in cancer cells along the pelvic wall. It is these outlying cells that must be reached and destroyed or recurrence is certain. Irradiation is the most important factor in attaining success in this concerted attack on the outlying cancer cells. There are exceptional conditions in which operative work with the knife also may be advisable, but, wherever used, operation should supplement irradiation and not displace it. Too many of these patients are still being treated with half-way measures, with operations that never reach the outlying cancer cells, and inefficient irradiation treatments that carry no devitalization into the distant cervical zone. Meigs[16] gives 5 reasons why he has resumed the operative treatment of cervical cancer. They are as follows: (1) if the cervix has been removed there is no chance for a recurrence in it; (2) if the cervix has been removed no cervical cancer can re-grow in it as a reoccurrence; (3) certain cancers of the cervix are radiation-resistant—a fact proved at the Pondville Hospital, where multi-

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ple biopsies are performed at the time the Roentgen ray and radium treatment are being carried out; (4) there will be less damage to the bowel if surgery is undertaken; (5) from the work of both Bonney and Taussig it is obvious that patients with lymph node metastases can be cured by surgery in some instances, and the author believes that it is not possible to cure, with radiation, cancer in lymph nodes deep in the pelvis. The surgery must be limited to certain types of patients; ideally they should be thin, young, in good health, and have an early growth. One other group has been operated upon and will be discussed separately in the statistics and results. These are the patients in whom one or two radiation attempts at cure have failed. These cases are non-elective and are "must" cases, and the results would be expected to be poor, and they are.

The preparation of the patient for operation is very important. This consists of admitting the patient to the hospital 4 to 5 days before the operation is to be done. The blood chemistry must be brought to normal, vitamins are supplied in large amounts to arrive as far as possible at a normal level, and blood transfusions are commonly given. Two days before operation, the patient is started on 1 gm. of sulfadiazine every 4 hours. The blood level has been determined in the beginning and is usually found at 6 to 8 mg. per 100 cc. Lately, the sulfadiazine has been given without determination of the level. At operation, 4 gm. of sulfanilamide are placed in the large pelvic defect under the new peritoneal floor. Sulfadiazine is continued by mouth as soon as the patient can take it, and is continued for 7 days after operation. Of 47 selected cases, none has died, an operative mortality of zero. It was essential in this series that the mortality be low, for the results with radium in the radiated cases are so good that a 10 to 20% would prohibit surgery. A mortality of 0%, or a very low mortality, gives the operator a feeling that at least he is as well off as is the radiologist in treating this type of disease. The most significant complications are difficulties with the urinary tract. Cystitis, dilated ureters, and hydronephroses are the rule after operation, not the exception. In most cases, an intravenous pyelogram taken before discharge will show large ureters and kidney pelves, but this condition will clear up. Occasionally, patients have difficulty in voiding or emptying the bladder due to injury to the sympathetic or parasympathetic nerves. In 5 (10.6%) of the 47 cases, ureteral fistulas developed, which in all cases will mean ultimate nephrectomy. This is a serious complication, but not a fatal one. In 1 patient with a huge tumor, both ureters were injured. There have been no vesicovaginal fistulas. The bladder was opened once and it was closed without any ill-effect. In 8 (17%) cases, lymph nodes were found to be positive; iliac nodes in 4, ureteral nodes in 1, and obturator nodes in 5. It is extremely important, however, to realize that 8 of these patients with very early lesions would have eventually died if radiation had been used. In this group with positive nodes, only 1 patient has succumbed so far. Of the 6 patients with recurrent disease or non-elective cases in whom operation was forced upon the surgeon, 5 have died, and 1 died of general peritonitis after operation. This is the only death in the series and, adding the groups together, makes 1 death in 53 patients (1.9%). It is interesting to note, and of real importance, that the patient who died was the only one of the entire series who was not prepared with a sulfonamide. Enough time has not elapsed to make the end-results of any value, but 5 are alive over 3 years; 4 over 2 years; 13 over 1 year; and the others for varying months under 1 year. Of the elective cases, 3 died of cancer. One died of cancer of the lung 2 years and 2 months after operation, and 1 died of generalized metastases

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throughout the body. He believes that surgery in selected cases is a better way to treat cervical cancer than is radiation. The experience of the patients who have had both methods of treatment has always been that the surgery was much easier to tolerate than the radiation. Surgery of this extensive type can be done safely if we take advantage of all the precautions of modern surgery. The preparation of the patient, the maintenance of good diet, hygiene, the correction of blood chemistry, the use of transfusion, and especially the use of sulfonamides make for safer surgery. This series demonstrates that, in the hands of one surgeon, nearly 50 selected patients were put through a grueling operative procedure without mortality. If it were not for injury of the ureter, it would probably be safe to say that this operation is better than radiation, but a ureteral injury of 10% in early cervical cancer is too large.

For over 10 years Taussig[24] has practiced the removal of the iliac lymph glands in addition to irradiation of the primary tumor in Group 2 cancer of the cervix, and has done 175 of these operations. He believes that the Wertheim operation with gland removal is the best procedure in the majority of early Group 1 cases. For persons untrained in the technique of the radical hysterectomy, he believes it safer and better to do the lymph gland operation with radiation of the cervix rather than an extensive Wertheim procedure. Hemorrhage was not infrequently an operative complication, especially since wider dissections have been practiced. In 11 patients, the hemorrhage was disturbing, but in no case was it fatal. Almost always the bleeding originated in the plexus of veins at the point where the internal iliac vein divides into its branches. These veins are very friable. In the first cases, he tried to catch these veins with forceps and attempted to pass a needle with ligature around them. Invariably the needle would puncture another vein and the bleeding increased. Three of the earlier cases of severe hemorrhage were left open, with clamps and a gauze pack to control the bleeding. Clamps and gauze were removed in 48 to 72 hours. Recently the cases have been handled far more successfully by a firm gauze pack with a strip of the rectus abdominis muscle applied against the bleeding area to promote coagulation. In 15 to 20 minutes the bleeding was usually controlled, and the operation could be concluded. In 2 cases a small gauze pack was left in the broad ligament for 48 hours. In the remaining cases, the bleeding was fully controlled and the pack removed before closure. This excessive bleeding can usually be avoided by more gentle manipulations in the deeper portions of the broad ligament. Injuries to important viscera or nerves are rare. The bladder is out of the operative field. The ureter must be watched, especially if large cancerous glands are present, as it may then be adherent to them and stripped off of its normal attachment to the posterior sheath of the peritoneum. Once he ligated the ureter but without harmful result to the patient. Once the obturator nerve was resected with an adherent obturator gland, but produced only temporary discomfort.

The percentage of 5-year survival was over 15% better in patients who had the additional procedure of iliac lymphadenectomy; or, to put it from the standpoint of patients saved, over 68% additional were saved by this operation.

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PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF OCTOBER 17, 1944

The Effect of Quinones on Blood Pressure in Hypertensive Rats. W. M. ZIEGLER and HENRY SCHWARZ (Philadelphia Institute for Medical Research, Phila. Gen. Hosp.). In a recent study Henry Schwarz and W. M. Ziegler found that 2-methyl-1,4-naphthoquinone considerably lowers the blood pressure of rats made hypertensive by silk perinephritis, and that a hydroquinone compound with similar vitamin K activity (*e. g.*, Synkayvite) does not produce any depression of blood pressure at all. (*Proc. Soc. Exp. Biol. and Med.*, **55**, 160, 1944.) The present studies were undertaken in order to investigate whether a definite chemical structure of p. quinones might be essential for their effect on blood pressure in hypertension. We also wanted to examine whether hydroquinones act differently, as was to be assumed from the 1 compound investigated. Our studies were performed in rats made hypertensive by wrapping both kidneys with silk. Eighteen different compounds, 14 quinones and 4 hydroquinones, many of them prepared in our laboratory, were assayed. The substances were dissolved in oil and given daily by intramuscular injection. The blood pressure was measured before, throughout and after the whole period of the experiment. Altogether 90 animals were used for the assays. The results of these studies are given in the following table:

ACTIVE DEPRESSORS	INACTIVE
Toluquinone	Quinone
p. Xyloquinone	2,3-dimethyl-Benzoquinone
m-Xyloquinone	Duroquinone
Thymoquinone	2,5-diethyl-Benzoquinone
-Naphthoquinone	Anthraquinone
Menadione	Tetrahydro-Naphthoquinone
2-ethyl-1,4-Naphthoquinone	2,3-dimethyl-Naphthoquinone
	Toluhydroquinone
	m-Xylohydroquinone
	Thymohydroquinone
	Synkayvite

From these studies it becomes clear that 1 hydrogen and 1 alkyl group are essential for the depressor effect of quinones in experimental hypertension. These radicals have to be at an essential place, *e. g.*, on the same half of the oxidized benzene ring imaginarily divided in a vertical direction.

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The type of the alkyl group might be of importance since the 2,5-diethyl-benzoquinone does not show any effectiveness, while the corresponding p. Xyloquinone is a powerful depressor. The effectiveness of the 2-ethyl-1, 4-Naphthoquinone might probably be explained by a change of the ethyl into a methyl group in the body. The -Naphthoquinone, which also lowers the blood pressure, is the only compound so far tested which does not show the essential structure. It has to be pointed out, however, that this substance is relatively toxic and that the difference between the effective and toxic doses is relatively small in this case.

All of the 4 hydroquinone compounds tested were ineffective. Since at least for the Synkayvite a transformation of the hydroquinone into quinone has been proved recently for normal animals (D. A. Richert, *J. Biol. Chem.*, vol **154**, 1944) it might be assumed that in experimental hypertension the oxidative transformation of hydroquinones into quinones is disturbed.

A Bacteriolytic Substance Contained Within a Purified Bacterial Virus. T. F. ANDERSON (Johnson Foundation, Univ. of Penna.). Centrifugally purified preparations of the tadpole-shaped bacterial virus γ have been found to lyse suspension of the host (*E. coli* strain B) which have received so much ultraviolet irradiation that multiplication of the virus does not occur. Moreover, such lysis proceeds immediately upon addition of virus to the host cells; this is in contrast to lysis of normal cells by virus which occurs only after a definite time interval in which the virus multiplies within the host cell. It thus appears that the virus has the ability to dissolve some substance or substances which hold heavily irradiated cells together. Disintegration of the virus particles by sonic vibration or by ultraviolet light fails to destroy the lytic activity, but rather enhances it.

Indeed, ultraviolet irradiation of the virus frees the lytic principle from the sedimentable material, for the activity of irradiated preparations remains in the supernatant even after centrifugation at 100,000 x gravity for 1 hour. The virus lysin may be similar to lysozyme for this enzyme also lyses heavily irradiated cells of *E. coli* B. However, the virus lysin appeared to be more specific in its action, for it exhibits no visible effect on *M. lysodeikticus* on which lysozyme is most active. Like lysozyme it is inactivated by 0.00001 N iodine and is not inactivated by 0.125 M Na_2AsO_3, 0.06 M NaN_3 or 0.125 N Na_2SO_3. $MgCl_2$ at 0.05 N inhibits its action either by an action on it or on its substrate.

The Quantitative Determination of Cerebral Blood Flow in Man by the Use of Nitrous Oxide in Low Concentrations. SEYMOUR S. KETY and CARL F. SCHMIDT (Dept. of Pharmacol., Univ. of Penna., and Med. Services, Phila. Gen. Hosp.). The proposed method is an application of the familiar Fick principle to the brain during its absorption of an indifferent gas from the blood passing through it. The relationships implicit in this principle may be expressed thus: cerebral blood flow (as cc. of blood per unit mass of brain tissue over any time period) is equal to the quantity of any gas taken up by unit mass of brain tissue during the same interval, divided by the quantity of that gas lost per cc. of blood during that period.

The experimental procedure involves the administration by inhalation of a gas mixture containing nitrous oxide (15%), in oxygen or a mixture of oxygen (21%) and nitrogen (64%). From needles inserted in the internal jugular vein and the femoral artery simultaneous pairs of blood samples are taken at 2, 4, 6 and 10 minutes after the onset of inhalation

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of the mixture. From the respective nitrous oxide concentrations it is possible to calculate the integral of the nitrous oxide arteriovenous difference over the 10-minute period which represents the quantity of gas lost to the brain per unit volume of blood during that time. The quantity of nitrous oxide taken up by the brain in that time is calculated from the internal jugular concentration of nitrous oxide in the 10-minute sample and from the partition coefficient of nitrous oxide between brain and blood.

The theoretical steps involved in this derivation have been subjected to experimental verification in monkeys, dogs and human subjects. Final proof of the validity of the method has been obtained by a comparison with values for cerebral blood flow obtained simultaneously in rhesus monkeys by direct measurement using the bubble flow meter (*Am. J. Physiol.*, **138**, 421, 1943). In 9 such comparisons the mean deviation between the two methods was $\pm 10\%$.

By means of this method cerebral blood flow and cerebral oxygen consumption have been measured in 8 human subjects representing 2 normal adults and 6 patients with various diseases. The values have fallen within a fairly close range. In the 2 normal subjects cerebral blood flow was 66 and 56 cc./100 gm./minute and cerebral oxygen consumption 4.4 and 3.7 cc./100 gm./minute respectively. These values are in excellent agreement with the averages recently reported for the rhesus monkey by the use of the bubble flow meter: cerebral blood flow 47 cc./100 gm./minute and cerebral oxygen consumption 3.7 cc./100 gm./minute (Am. J. Med. Sci., **207**, 813, 1944). For a normal human brain weighing 1300 gm. the values obtained by the nitrous oxide method would yield a total cerebral blood flow of 780 cc./minute and a cerebral oxygen consumption of 52 cc./minute.

Even 15% nitrous oxide is not completely inert physiologically and might conceivably influence cerebral blood flow. This disadvantage may be overcome by the use of a radioactive inert gas instead of nitrous oxide.

A Further Study of the Innervation of the Pancreas—The Action of Drugs of the Atropine Group. J. E. Thomas and J. O. Crider (Laboratory of Physiology of the Jefferson Medical College). The secretory response of the pancreas to peptone, soap, or HCl in the intestine or to intravenous secretin was studied in unanesthetized dogs before and after administration of atropine or hyoscyamine. The usual dose of atropine (sulfate) was 0.2 mg. and of hyoscyamine (hydrobromide) was 0.1 mg. per kilogram.

The specific gravity and total N (mg./cc.) of the pancreatic juice were decreased by the action of these drugs regardless of the stimulus used to promote secretion. When the stimulus was soap, HCl, or secretin the volume of the secretion and total nitrogen output were also reduced. When the stimulus was peptone an increase in volume of secretion usually followed administration of either drug; the effect on total nitrogen output was not constant but an increase was common.

The fact that the parasympathetic depressants decrease the response to secretin is surprising and contrary to results obtained by others in anesthetized animals. Probably "tonic" cholinergic reflexes normally augment the response to secretin in unanesthetized animals. The results with soap and HCl indicate that these agents stimulate the pancreas in part through a nervous mechanism. The experiments provide no basis for conclusions regarding the mechanism through which peptone stimulates the pancreas.

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BOOK REVIEWS AND NOTICES

TECHNIC OF ELECTROTHERAPY AND ITS PHYSICAL AND PHYSIOLOGICAL BASIS. By STAFFORD L. OSBORNE, M.S., PH.D., Assistant Professor, Department of Physical Therapy, Northwestern Univ. Med. School, and HAROLD J. HOLMQUEST, B.S., B.S.(M.E.), Lecturer in Applied Physics, Department of Physical Therapy, Northwestern Univ. Med. School, Chicago. Pp. 780; 240 figs.; having 293 illus., 72 tables. Springfield, Ill.: Charles C Thomas, 1944. Price, $7.50.

THIS new work is the outgrowth of numerous requests from the authors' students. It is divided into 4 parts: direct current, electrical stimulation of muscle, radiation, and high-frequency currents. It is one of those not-so-common books which serve not only as a reference text but also as a laboratory guide and manual. The first part in particular is well designed for the latter purpose. A short historical survey precedes many of the sections. Fundamental principles are outlined in simple form for the benefit of beginners; foot-notes, tables, and mathematical formulæ are appended for the more advanced students. References to literature appear at the bottom of pages.

There is a tendency to some unevenness in the space allotted to various subjects; a discussion of coal tar as a sensitizing agent prior to the use of ultraviolet occupies 2 pages while the biologic effects of ultraviolet occupy a bare 13 pages. The magazine *Time* attains bibliographic stature, as in the discussion of fluorescence; a "personal communication" from the authors whose work was cited would have been more appropriate. Over 400 pages are devoted to the portion dealing with high-frequency currents; the discussion of artificial fever is excellent. Short summaries at the end of sections are an added feature. Illustrations are clearly reproduced, numerous and well chosen. Type face, setting, and a thin glossy paper make the whole "eye easy" and very compact.

This contribution to an important aspect of physical medicine is warmly recommended. M. B.

TECHNICAL METHODS FOR THE TECHNICIAN. By ANSON LEE BROWN, A.B., M.D., Director of Dr. Brown's Clinical Laboratory and Dr. Brown's School for Technicians, Columbus, Ohio. Pp. 706. Third Ed. 229 figs. Published by the Author, 1944. Price, $10.00.

THIS text comes from the Author's school for technicians. In content and style it seems designed for the average high school graduate lacking much background in science. The vocabulary is simple; elementary procedures are described in detail; technical terms are defined in abundance; and review questions are listed at the end of each chapter. Good instructions are given for such beginner problems as operation of a microscope, handling of reagents, chemical filtration, weighing with a balance, use of a counting chamber and taking of a basal metabolism test. There are many good line illustrations and several color plates of the blood cells and of blood groupings. Directions are offered for performing 8 different serologic tests for syphilis, including an original micro-precipitation technique, "presented for the first time," based on extracted powdered beef testicle as the antigen. The blood chemistry chapter is well done, but the sections on feces examination, gastric analysis and semen study are inadequate. Bacteriology and electrocardiography are not discussed. Erroneous statements abound, such as: "the slightest trace of albumin in the urine is considered abnormal" (!); "the normal specific gravity for urine is usually given as 1.012 to 1.020" (a narrow nephritic range!); when doing Benedict's test for sugar in urine "heat for not over 10 to 15 min-

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utes" (much too long!); with the Westergren blood sedimentation test, "above 6 or 7 mm. is pathological" (customary accepted limits are about 15 mm. for men, 20 mm. for women). No space is given to pentosuria, recognition of the cells of infectious mononucleosis, the dark-field test for spirochetes, and other valuable methods. This book may find some application in the office of a doctor himself skilled in basic principles, who is teaching his secretary to assist in laboratory procedures, but it cannot be recommended to physicians or technicians as an authoritative reference. I. W.

MANUAL OF PSYCHOLOGICAL MEDICINE. For Practicioners and Students. By A. F. TREDGOLD, M.D., F.R.C.P., F.R.S.E., Consulting Physician to Univ. College Hosp., London Lecturer on Mental Deficiency, London Univ. Pp. 298. Baltimore: Williams & Wilkins. Price, $5.00.

THIS short but comprehensive textbook of psychiatry comes to us from England. The psychoneuroses, epilepsy, mental disorders and mental defects are described in successive chapters. In addition, there are chapters on psychopathology, psychotherapy, and the legal aspects of psychiatry. The author, who appears to have a special interest in mental deficiency, expresses this orientation by espousing the idea that "germ corruption" or blastophoria, is a causative factor in psychiatric disorders. He makes much of terms such as "constitutional mental instability," "constitutional predisposition" (to mental disease), "poor mental stamina," etc. He warns against psychoanalysis, and dismisses Freud as one whose work, although having a revivifying effect, largely consisted in the bestowal of new names on old concepts. "Unfortunately," he adds, "Freud seems to have been obsessed by sex." There is a section on neuroses and psychoses in soldiers, which is also marred by the author's reactionary psychopathologic theories. D. P.

THE MANAGEMENT OF NEUROSYPHILIS. By BERNHARD DATTNER, M.D., JUR.D., Associate Clinical Professor of Neurology, New York Univ. Medical College. With the collaboration of EVAN W. THOMAS, M.D., and GERTRUDE WEXLER, M.D. Foreword by JOSEPH EARLE MOORE, M.D. Pp. 398; 40 figs., charts, tables. New York: Grune & Stratton, 1944. Price, $5.50.

IN the first part, the Author discusses the techniques of withdrawing and examining spinal fluid and the interpretation and evaluation of changes occurring therein. He brings support to those who believe that spinal punctures can be safely done on the ambulatory patient. His experience has been that, providing the puncture is skilfully done with a narrow gauge needle (he prefers his double needle) and 10 cc. or less of fluid is removed, the patient has less chance of a headache if he remains active.

He emphasizes that changes in the spinal fluid are frequently found without clinical manifestations, and that there is no constant spinal fluid picture diagnostic of particular clinical entities. Dattner agrees with other workers on syphilis that the age of the infection and the influence of treatment are important factors in the prognostic interpretation of spinal fluids. He states that the finding of a negative spinal fluid in a case of at least 4 years' duration, and untreated for 6 months prior to the examination, is almost absolutely certain to remain negative.

In the second part the Author discusses all the methods of treating neurosyphilis. Some forms with meningeal involvement respond well to ordinary intensive chemotherapy. He favors fever therapy, preferably with malaria, followed by intensive chemotherapy for a short period for such cases that prove resistant to the above, and as first choice in the more serious types of cerebrospinal involvement. If the febrile response to malaria is good, he favors from 8 to 10 paroxysms, followed immediately by 10 daily injections of 0.06 gm. of mapharsen.

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This book is interesting and easy to read. It reviews the subject in comprehensive manner and should be useful to anyone working in the field of neurosyphilis. R. R.

THE ART OF ANÆSTHESIA. By PALUEL J. FLAGG, M.D., Visiting Anesthetist to Manhattan Eye and Ear Hosp.; Consulting Anesthetist to St. Vincent's Hosp., New York, N. Y.; Consulting Anesthetist to the Women's Hosp., Sea View Hosp., Jamaica Hosp., Mount Vernon Hosp., Flushing Hosp., Mary Immaculate Hosp., St. Mary's Hosp., Far Rockaway, N. Y.; Nassau Hosp., L. I.; Director of Pneumatology, World's Fair, New York City, and Chairman of Committee on Asphyxia of the American Medical Association. Seventh Ed. Pp. 519; 166 illus. Philadelphia, London, Montreal: J. B. Lippincott Company, 1944. Price, $6.00.

THIS book is in no sense a comprehensive treatment of the subject. The Author's known preference for ethyl ether is evident throughout. Some of the major advances in anesthesia such as the technique of continuous spinal, the use of pentothal intravenously, and of cyclopropane by inhalation are dismissed as innovations or as being too recent for evaluation. While no one can deny the widespread usefulness of ether, unless it be clearly regarded as one individual's personal opinion, a text on anesthesia should be broader in scope, and more tolerant. Spinal anesthesia is a valuable adjunct to surgery and anesthesia, yet this commonly employed method is treated in 13 sketchy pages.

Despite the imbalance of the presentation, it is interesting to read of the Author's experience with ether. His approach to the signs of anesthesia is quite different from the standard, yet the careful student can learn much, for the topic is covered in detail. As a record of personal feelings, the volume can be recommended, but as a broad approach to the field of anesthesia, there are omissions which can be questioned. R. D.

A TEXTBOOK OF HISTOLOGY. Arranged Upon an Embryological Basis. By J. LEWIS BREMER, M.D., Hersey Professor of Anatomy, Harvard Univ. Rewritten by HAROLD WEATHERFORD, PH.D., Assistant Professor of Anatomy, Harvard Univ. Sixth Ed. of "Lewis and Stohr." Pp. 723; 598 illus. Philadelphia: Blakiston, 1944. Price, $7.00.

THE material covered in this new edition embraces the whole meeting ground of Histology and Embryology. The traditional aspects of Histology have not been neglected but the ideas of previous authors are supplemented with a vast amount of information collected from the works of investigators of recent years. The classical point of view and modern ideas are brought successfully into harmony. Fundamental questions on Embryology are very clearly presented. Over 300 new carefully selected and very instructive figures have been added in this edition.

In every part and detail this is a modern textbook of Histology and may be recommended to medical students and to physicians as a good reference book for their bookshelf.

The authors, co-authors and the publishers have produced a book that will be very popular among students and teachers in Histology. G. DE R.

PRINCIPLES AND PRACTICES OF INHALATIONAL THERAPY. By ALVAN L. BARACH, M.D., Associate Professor of Clinical Medicine, Columbia College of Physicians and Surgeons; Assistant Attending Physician, Presbyterian Hospital. Pp. 315; 59 figs. Philadelphia: J. B. Lippincott, 1944. Price, $4.00.

THIS, the first volume of its kind in medical literature, is written by one who has pioneered in the field of inhalation therapy. The physiologic basis

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for such treatment is thoroughly presented in chapters dealing with pneumonia, pulmonary edema, coronary artery disease, atelectasis, asthma and emphysema. The implications of anoxia are also stressed in a number of conditions with which physicians are less familiar, *e. g.*, blast injuries, caisson disease, aerial transporation, head injuries, fever therapy. Practical details are given in addition to the excellent theoretical discussions. The various methods of inhalation therapy are outlined. A chapter on respirators is useful. Positive pressure techniques, the use of nebulized solutions of various drugs and other recent advances in the treatment of respiratory disorders are all carefully presented.

The book should prove stimulating to the respiratory physiologist, internist, anesthetist and surgeon. R. D.

UROLOGICAL SURGERY. By AUSTIN INGRAM DODSON, M.D., F.A.C.S., Professor of Urology, Medical College of Virginia; Urologist to the Hospital Division, Medical College of Virginia; Urologist to Crippled Children's Hospital, St. Elizabeth's Hospital, St. Luke's Hospital and McGuire Clinic. With contributions by 7 well-known authorities. Pp. 768; 576 illus. St. Louis: C. V. Mosby, 1944. Price, $10.00.

SPECIAL emphasis on the surgical treatment of urologic conditions is made in this new book. The author states that his purpose is to present information on surgical problems arising in practice, as a surgical supplement to the many excellent books already written on the principles and practice of urology.

Anatomy of the genito-urinary tract, with special reference to surgical considerations, is presented. Throughout the text, preoperative and postoperative treatment, so essential to good results in urologic surgery, is emphasized. There are chapters on excretion urography and cystography, radiation therapy, acid-base balance, fluid administration, blood transfusion, anesthesia, and endocrinology. Each of these chapters is written by an author who is a specialist in the respective field. Surgical problems are discussed in anatomic sequence, beginning with the kidney and followed by adrenal, ureter, bladder, urethra, perineum, penis, scrotum and testicle. Diseases of the adult male and female, as well as diseases in children are presented.

Illustrations are good. Those showing the technic of certain operative procedures are particularly well presented. Each chapter is followed by a bibliography. References are made to the most recent literature.

This book should be of particular value to urologists, and general surgeons; it should also be an excellent reference book for medical students and general practitioners. L. LaT.

THE ART AND SCIENCE OF NUTRITION. A Textbook on the Theory and Application of Nutrition. By ESTELLE H. HAWLEY, PH.D., and GRACE CARDEN, B.S., The Univ. of Rochester, School of Medicine and Dentistry, Strong Memorial and Rochester Municipal Hospitals, Rochester, N. Y. Second Ed. Pp. 668; 139 illus. (11 colored); 138 figs.; 68 tables. St. Louis: C. V. Mosby, 1944. Price, $3.75.

As the title suggests, this book deals not only with the basic principles of nutrition, but also goes into great detail to demonstrate how best to apply the principles to everyday living and to the special needs of diet therapy.

It is focussed especially on teaching of dietetics in schools of nursing, but it would be a most useful reference book for the practitioner of medicine as well. One section of the book is devoted to food requirements under special conditions, such as pregnancy and its complications, lactation, the feeding of infants and young children, diet in relation to the teeth, and the food requirements of old age. Diet therapy is treated at length. A practical laboratory course of 20 lessons on the choice, preparation, and serving of foods is included. Illustrations are numerous and excellent. E. W.

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FERTILITY IN MEN. By ROBERT SHERMAN HOTCHKISS, B.S., M.D., LT. COMM. (M.C.), U.S.N.R. (on active service), Assistant Professor of Urology, New York Univ. Medical College; Instructor in Surgery (Urology), Cornell Medical College; Assistant Visiting Attending Physician, Department of Urology, Bellevue Hospital; Assistant Visiting Attending Physician in Surgery (Urology), New York Hospital; Chief of Urological Clinic, New York Univ. Medical College Clinic. Foreword by NICHOLSON J. EASTMAN, M.D. Pp. 216; 95 illus. Philadelphia: J. B. Lippincott, 1944. Companion book to "Fertility in Women." Price, in slip case, $8.00.

THE book presents a clinical study of the causes, diagnosis, and treatment of impaired fertility in the male. It is issued as a companion volume to "Fertility in Women," by S. L. Siegler.

Until recent years the blame for sterility in marriage was almost always placed on the wife. However, during the past 2 decades accumulative information would indicate that many cases of sterility in a family group are due to diseases in the male. The discovery that sterility in the male was widespread opened a new field of study and treatment in urology. This volume presents such information on the problems associated with male sterility in a concise, well-organized manner.

With special reference to fertility, anatomy, physiology, and pathology of the male genital organs are discussed. Much new information on the metabolism of spermatozoa and the chemical composition of semen is presented. Practical methods of appraising fertility in the male are recorded. The technics and interpretation of clinical laboratory studies of spermatozoa and semen are given in detail. No other reference book need be consulted in order to carry out such methods satisfactorily. There are several case histories illustrating various types of sterility and emphasizing not only the anatomicopathologic entities, but also the psychic aspects of cases besides. Medical and surgical methods of treatment of the various entities are discussed in detail. Excellent illustrations appear and each chapter is followed by a liberal bibliography.

Future therapy in diseases causing sterility depends on advances in glandular physiology, enzymic chemistry, nutrition, and cytology. Advances in the laboratory must be applied to treatment of the patients. Sterile patients, successfully treated, are most grateful. L. La T.

THE ROMANCE OF MEDICINE. The Story of the Evolution of Medicine From Occult Practices and Primitive Times. By BENJAMIN LEE GORDON, M.D., Member, Am. Assn. of the Hist. of Med.; Attending Ophthalmologist to the Shore Memorial Hospital, Somers Point, N. J., and to Atlantic County Hospital for Tuberculosis, Northfield, N. J. Authorized Medical Examiner for Civil Aeronautics Administration, Dept. of Commerce, Washington, D. C. Formerly Associate Ophthalmic Surgeon of St. Agnes Hospital of Philadelphia. Pp. 624; 147 illus. Philadelphia: F. A. Davis, 1944. Price, $5.00.

THOUGH this entertaining volume touches throughout on medical matters from the historical point of view, it is in no sense a history of medicine, whether biographic, topic, or chronologic—nor is it intended to be so. Starting with primitive man's concepts of life and disease, the author aims to trace the evolution of these concepts into the corresponding ideas of today. This plan leads to 26 chapters on such subjects as Fecundation and Gestation, Galenic Physiology, The Vital Principle, Demonology, Astrology, The Evil Eye, Spiritual Healers, Scapegoats, Mystic Medicine, "Signatures," Primitive Healing Measures, Ancient Ethics, Ideas of After Life. One might infer from such a list that superstitions would fill most of the book. Not only is this the case, but in telling about them the author is at his best; the change to a brief consideration of modern practices usually being more of a jump than a gradual progress.

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One adds regretfully that illustrations are mostly on hackneyed subjects and are poor specimens, also that there is but little use of original sources; and one who is annoyed by poor spelling will be frequently annoyed. (The Reviewer found 18 such errors in less than an hour's reading.) Nevertheless, the book contains much interesting information about primitive and ancient customs related to medicine, and should afford pleasant and instructive reading to those curious about such matters. E. K.

FERTILITY IN WOMEN. By SAMUEL L. SIEGLER, M.D., F.A.C.S., Attending Obstetrician and Gynecologist, Brooklyn Women's Hospital; Attending Gynecologist, Unity Hospital; Assistant Obstetrician and Gynecologist, Greenpoint Hospital; Attending Sterility Clinic, Greenpoint Hospital; Consultant in Gynecology, Rockaway Beach Hospital; Diplomate, Am. Board of Obstetrics and Gynecology; Fellow, New York Academy of Medicine; Member, Soc. for the Study of Internal Secretions. Foreword by ROBERT LATOU DICKINSON, M.D. Pp. 450; 194 illus. Philadelphia: J. B. Lippincott, 1944. Companion book to "Fertility in Men." Price, in slip case, $8.00.

THIS treatise on the causes, diagnosis, and treatment of impaired fertility in the female is a companion volume to "Fertility in Men," by R. S. Hotchkiss, M.D. A consideration of the problems associated with both male and female aspects of sterility, the author's so-called "bilateral approach" is stressed throughout the book.

Knowledge of the factors responsible for both male and female fertility has advanced considerably in the past 2 or 3 decades. Studies in the biology, chemistry, physiology, and psychiatry of human reproduction and sex adjustments have aided greatly in furthering this knowledge. Methods of evaluating fertility in the laboratory, as well as special points in history taking and physical examination are presented. This information would enable one to make a true evaluation of the case at hand.

There are chapters on the physiology of the female sex cycle, cervical and and vaginal secretions and their relation to spermatozoa, and tubal factors in sterility. Endocrine disorders in which sterility occurs are thoroughly discussed. The present methods of medical and surgical treatment of such conditions as are amenable to therapy are discussed.

The purpose of the book is to present a description of the anatomic and physiologic factors in sterility encountered in medical practice. It covers the subject of the females' part in sterility completely, and along with its companion volume, "Fertility in Men," makes an important contribution to recorded knowledge on this subject. L. LaT.

THE MEDICAL CLINICS OF NORTH AMERICA, March, 1944. Symposium on Chronic Diseases. Pp. 516. Philadelphia and London: W. B. Saunders. Price, $16.00, year.

THE contributors to this volume show a practical, lucid, and up-to-date approach to the subjects chosen, place much emphasis on treatment, and have succeeded to an unusual degree in combining the newer therapeutics with such older methods of treatment as have stood the test of time.

The introduction by R. L. Cecil makes clear the prevalence of chronic disease in the younger age groups. Far from finding chronicity synonymous with old age, we discover in the New York City studies that nearly half the chronically ill patients were under 40 years of age, about a third being children under 16.

Discussions on present-day treatment of *syphilis* and of *gonorrhea* occupy the first and the last places in this volume. Experience now accumulated with short-term arsenotherapy is reviewed. A rational treatment for gonor-

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rhea, combining the use of sulfonamides with older forms of treatment, is outlined. In both of these discussions one catches a hint of the temporary, and the impression that penicillin, when generally available, may be the answer to the search for a quick treatment for early syphilis and for gonorrhea.

Chronic arthritis is the most prevalent of all chronic ailments. For *rheumatoid arthritis*, various forms of therapy are evaluated, and especially the results to date of therapy with vitamin D and with gold. The dangers of toxic manifestations are outlined.

Accepted methods for treating chronic *diseases of nose, throat* and *ear* are presented. A few well-chosen case reports serve to illustrate pitfalls in the diagnosis and treatment of *diseases of the larynx and trachea.* Treatment for the refractive case of *bronchial asthma* is detailed, including methods of inducing cumulative relaxation of the bronchial musculature by repeated use of aminophyllin intravenously or by rectum.

An especially helpful paper dealing with the chronic anemias points out the fallacy of attempts at treatment without proper diagnosis, and gives in outline form the studies required for adequate diagnosis, and the classification of the anemias based on etiology and morphology. A brief paper on *renal insufficiency* usefully directs attention to reversible causes and the importance of search for such causes in all cases not definitely assignable to the irreversible group.

The medical management of *peptic ulcer* is discussed on the basis of a large clinical experience. Simplification of treatment to the point where the average patient relies primarily on food and mode of life, and little or not at all on medication, will be found a boon to patient and physician alike. *Functional disturbances of the alimentary tract* are reviewed. There are helpful discussions on the management of *heart disease;* the management of *diseases of the nervous system,* and chronic *endocrine disorders,* including a special paper on the difficult problem of exophthalmos in Graves' disease.

Not the least useful feature of the whole collection of papers is the carefully selected list of references attached to each. The physician will find this volume a convenient and reliable guide and will welcome the wealth of practical suggestions for the handling of some of man's most difficult ailments.

J. M.

INTRAVENOUS ANESTHESIA. By R. CHARLES ADAMS, M.D., C.M., M.S. (ANES.), Associate in Section on Anesthesiology, Mayo Clinic; Instructor in Anesthesiology, Graduate School University of Minnesota, Rochester, Minn. Foreword by DR. JOHN S. LUNDY. Pp. 663; 34 tables; 75 figs. New York, London: Paul B. Hoeber, 1944. Price, $12.00.

THIS book gathers under one cover a good bit of interesting and useful information about the intravenous administration of various narcotics. Ether, paraldehyde, alcohol, and magnesium sulfate, have all been used in the past and occasional clinical articles are appearing now suggesting their value in various conditions. It is helpful to have detailed reference to the earlier development and present status of these agents. Incidentally, one would expect more data on the intravenous use of morphine.

The book represents an unusual attempt to review apparently every article ever written on the subject. In an introductory chapter on derivatives of barbituric acid, for example, 498 references are listed! In a chapter on Pernoston, a drug rarely used today, 303 articles are given. The intravenous anesthetic most commonly used in this country is pentothal sodium, and this agent is not considered until page 451. Whether the importance of the field justifies so inclusive a coverage remains for the individual leader to determine. It is perhaps doubtful as to whether 662 pages are necessary to adequately review the topic. In the preface the Author points out his awareness of the detailed nature of the presentation so that the Reviewer's criticisms are perhaps unjust.

R. D.

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THE YOUNGEST OF THE FAMILY. HIS CARE AND TRAINING. A Manual for the Inexperienced Mother. By JOSEPH GARLAND, M.D., Physician to Children's Med. Dept., Massachusetts General Hospital; Consulting Pediatrician, Massachusetts Eye and Ear Infirmary; Instructor in Pediatrics, Harvard Medical School. Revised Ed. Pp. 182. Cambridge, Mass.: Harvard Univ. Press, 1943. Price, $2.00.

DR. GARLAND is practical, conservative, learned and witty; and his "baby-raising" book is a polished expression of current pediatric thought. Advice on the many maneuvers of baby care is given in literary rather than cookbook style, which no doubt will confuse some readers and please others. The major defect in the presentation is the absence of a section on the preparation of milk mixtures and the sterilization of feeding equipment. Emphasis has been directed toward building up an understanding of the phenomena of infant and pre-school child behavior. This is, of course, of paramount importance, and the book may be recommended with assurance to intelligent parents who are desirous of that type of guidance. I. W.

THE PATHOGENESIS OF TUBERCULOSIS. By ARNOLD R. RICH, M.D., Associate Professor of Pathology, The Johns Hopkins University School of Medicine, Baltimore, Md. Pp. 1008; 89 figs.; 4 charts; 20 tables. Springfield, Ill.: Charles C Thomas, 1944. Price, $10.50.

RESEARCH in tuberculosis has progressively built up a tremendous literature over many years. Many of the older concepts have been amended or supplanted. Others, on which the evidence is still incomplete, or worse, contradictory, are in a state of flux. Because of his special interest in tuberculosis and his fine anatomic background, the author is admirably suited to attack this problem. He has produced a most valuable survey of the field with critical reëvaluation of many long accepted fundamental concepts.

The book begins with a discussion of the tubercle bacillus, its mode of action, as a whole and as isolated chemical fractions. Next, a large section is given over to the immunologic aspects of the disease, native and acquired resistance and hypersensitivity. Following this, in a discussion of the factors responsible for the tuberculous lesion, he gives a good account of the general pathologic anatomy and later, in a separate chapter, considers the special pathologic anatomy of certain organs (lung and meninges). As the emphasis is placed on pathogenesis no extensive anatomic descriptions are attempted.

The text reads easily despite profuse documentation. Throughout is evident the special care taken to provide references. The extensive bibliography (1417 references) should prove most valuable to those with special interest in any of the various controversial problems. The sections on resistance and hypersensitivity are recommended to students, teachers, and practitioners, as they help to clarify this complex subject. Especially convenient are the short summaries at the end of each section.

The book's most important contribution is that it provides the urgently needed correlation between the massive animal experimental researches and the disease as it occurs in man. W. S.

HYPERTENSION AND HYPERTENSIVE DISEASE. By WILLIAM GOLDRING, M.D., Associate Professor of Medicine, New York Univ. College of Medicine; and HERBERT CHASIS, M.D., Assistant Professor of Medicine, New York Univ. College of Medicine. Pp. 253; 53 figs.; 27 tables. New York: The Commonwealth Fund, 1944. Price, $3.50.

FOR those interested in keeping abreast of current thought regarding the nature of hypertension, this book will prove well worth reading. The authors review the pioneer clinical work in the study of differential aspects of renal physiology which they, in association with Dr. Homer W. Smith, have performed. Further, they present their present concept of hypertensive disease and its various ramifications.

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The book is divided into short, readable chapters. Illustrations and references are well chosen. Investigative techniques are described in sufficient detail to guide those who may wish to employ the elaborate, but ingenious procedures which these workers have developed. The authors conclude that no treatment yet devised is of avail in altering the slow but certain course of hypertensive disease. W. J.

SYSTEMATIC INORGANIC CHEMISTRY—THE FIFTH AND SIXTH GROUP NON-METALLIC ELEMENTS. By DON M. YOST, Professor of Inorganic Chemistry, and HORACE RUSSELL, JR., Instructor in Chemistry, California Institute of Technology. Pp. 423; 78 figs.; 109 tables. New York: Prentice-Hall, 1944. Price, $4.60.

IN this book the authors have selected a list of topics devoted to the fifth and sixth group non-metallic elements of the periodic system and "include in the discussion of each enough of the old and the new chemistry to bring out the most important features of the substances." In many cases the original literature references are included in the statements throughout the text. These guide the student seeking a detailed discussion of the point in question.

The methods of preparation and purification of the various substances are given. Both physical and chemical properties are included. Figures and tables, giving other pertinent data, are numerous.

In addition, the authors emphasize "the research point of view" by suggesting "many problems worthy of the serious attention of research workers."

The scope of the book as given by chapter headings follows: 1. Nitrogen and Its Oxides and Sulfides. 2. Nitrogen Oxyhalides and Oxyacids; Fixation of Nitrogen. 3. Hydroxylamine, Amine Sulfonites, Phosphorus Chloronitrides, Hydrazine, and Hydrazoic Acid. 4. Ammonia and Liquid Ammonia Solutions. 5. Phosphorus, Its Oxides and Sulfides. 6. Oxyacids of Phosphorus. 7. Phosphorus Halides and Oxyhalides; Phosphine. 8. Oxygen, Sulfur, Selenium, Tellurium, and Their Compounds With Hydrogen. 9. Halides and Oxyhalides of Sulfur, Selenium, and Tellurium. 10. Oxides and Oxyacids of Sulfur, Selenium, and Tellurium. 11. Hydrogen Peroxides, Persulfides, and Peroxyacids; Metallic Peroxides and Superoxides; Polythionic Acids.

In the Appendices are listed a bibliography of reference books, general physical constants, and the periodic system of elements.

The volume is well printed and easy to read. It contains complete subject and name indices. For a study of the specialized field of inorganic chemistry (fifth and sixth group non-metals) this book will serve as an excellent textbook or reference text. C. D.

REBEL WITHOUT A CAUSE. The Hypnoanalysis of a Criminal Psychopath. By ROBERT M. LINDNER, PH.D., U. S. Public Health Service (R) Psychologist, U. S. Penitentiary, Lewisburg, Pa.; Lecturer in Criminology, Bucknell Univ. Introduction by SHELDON GLUECK, LL.B., PH.D., Professor of Criminal Law and Criminology, Law School, Harvard Univ., and ELEANOR T. GLUECK, ED.D., Research Criminologist, Law School, Harvard Univ. Pp. 295. New York: Grune & Stratton, 1944. Price, $4.00.

BY combining the methods of psychoanalysis and hypnotism, this psychologist has evolved an original plan for the study of psychopathy as encountered in psychiatry and criminology. The method is termed hypnoanalysis, and is defined as "a radically abbreviated method for the investigation of the personality and the treatment of psychogenic disorders and aberrations of behavior." In speaking of the method, the writers of the Introduction state that they do not "know whether . . . . it will go beyond diagnostic dissection to permanent reconstruction of the personality."

The subject studied was in good health, except that following an attack of measles in infancy, he was left with what one specialist termed *nystagmus*

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amblyopia, and another, *congenital defective retinæ*. Disclosure of the lad's psychopathic personality came through the commission of numerous delinquencies and one stabbing affair. After taking a formal case history, the hypnotized subject's revelations were recorded during 46 sittings of 1 hour each. For the ready attainment of the trance state it is said a week may be required, but that, later, the state should be attained almost at once. After the induction of complete amnesia, all resistance is overcome and disclosure flows smoothly as various components of the psychoanalytic technique are applied.

Somewhat apologetically, the writer explains that while only 1 case is here hypnoanalyzed, he has had 5 others which likewise "demonstrated . . . . at least at the time of this writing of the benefits of treatment." In helping to solve the perplexing problem of the psychopathic personality, a courageous effort has been made through an original plan of analysis and reconstruction. A bibliography and index are included. N. Y.

ARTIFICIAL PNEUMOTHORAX IN PULMONARY TUBERCULOSIS. By T. N. RAFFERTY, M.D., formerly Resident Physician, William H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Mich. Introduction by HENRY STUART WILLIS, M.A., M.D. Pp. 192; 26 figs.; 14 tables. New York: Grune & Stratton, 1944. Price, $4.00.

THE title of this book, not indicating the true scope of the work, is apt to deflect from its usefulness. Although primarily a discussion of artificial pneumothorax, it covers the whole subject of collapse therapy in tuberculosis. By discussing the pros and cons of the various types of collapse therapy, an overall picture of the treatment and prognosis of the disease is presented. This is valuable both to the specialist and to the internist or family physician who directs the care of the patient. The latter, unfortunately, is apt to have too optimistic a point of view as to the prognosis. This book will once more acquaint him with the true dangers of the disease and the need for careful supervision of all cases.

The chapters on the importance of bronchoscopic examination and closed intrapleural pneumolysis are particularly good. These procedures are not in general use and too often are neglected because of the technical skill required. The section on the management of pneumothorax is full and complete and yet not too technical to be tiring. In fact, the entire book is well written and the subject matter pleasantly presented. D. P.

QUICK REFERENCE BOOK OF MEDICINE AND SURGERY. A Clinical, Diagnostic, and Therapeutic Digest of General Medicine, Surgery, and the Specialties. By GEORGE E. REHBERGER, A.B., M.D. Twelfth Ed. Pp. 1460. Philadelphia, London, Montreal, J. B. Lippincott, 1944. Price, $15.00.

THE fact that this book has reached its 12th edition in 24 years is good evidence of its continued popularity. Perhaps this is in measure to be explained by the relatively large amount of space devoted to methods of therapy. As regards the other aspects of medicine, surgery, and obstetrics the discussions are of necessity very sketchy. A physician with even a very modest library should have little need for books of this kind. H. S.

THE ANALYSIS AND INTERPRETATION OF SYMPTOMS. Edited by CYRIL M. MACBRYDE, M.D., and ten contributors. Reprinted from *Clinics*, Vol. **11**, No. 6, 1944. Pp. 301; numerous figs., tables and plates. Philadelphia: J. B. Lippincott, 1944. Price, $4.00.

THIS is an excellent book. Its excellence consists in its practical approach to clinical problems and the thoroughness with which each subject is presented. As MacBryde says in his introduction, a patient does not present

himself with a diagnosis but with a symptom. The ordinary textbook, however, classifies data according to diagnoses and not under symptom headings. Some older textbooks, like those of Butler and of French, adopted the latter system and were highly popular. This one should be more so because it does more than list the causes of nervousness, fatigue, headache, fever, cough, abdominal pain, etc.; it explains the mechanism involved, and in most instances this is done by one who has made significant contributions in the field that he presents. Many other symptoms and physical phenomena such as nausea, diarrhea, anemia, weight loss and lymphadenopathy, might well be the subjects for a subsequent presentation. Such books will appeal to medical students especially, but will also be welcomed by the practicing physician. Within themselves they are stimulating and they will lead to further intelligent perusal of the fundamental literature. T. M.

NEW BOOKS

Neurology of the Eye, Ear, Nose, and Throat. By E. A. SPIEGEL, M.D., Professor of Experimental and Applied Neurology and Head of Dept. of Experimental Neurology, Temple Univ. School of Med., and I. SOMMER, M.D., Lecturer in Ophthalmology, Long Island Coll. of Med.; Consultant Ophthalmologist and Otolaryngologist, Chicago Eye and Ear Hosp. Pp. 690; 118 figs. New York: Grune & Stratton, 1944. Price, $7.50.

Gynecological and Obstetrical Urology. By HOUSTON S. EVERETT, A.B., A.M., M.D., Associate Professor of Gynecology, the Johns Hopkins Univ., and Associate in Gynecology, The Univ. of Maryland; Assistant Visiting Gynecologist and Gynecologist in charge of the Cystoscopic Clinic, the Johns Hopkins Hosp.; Visiting Gynecologist, the Church Home and Hosp., the Hosp. for the Women of Maryland, and the Union Memorial Hosp. Pp. 517; 220 figs. Baltimore: Williams & Wilkins, 1944. Price, $6.00.

All About Feeding Children. By MILTON J. E. SENN, M.D., Associate Attending Pediatrician, New York Hosp., Associate Professor of Pediatrics in Psychiatry, Cornell Univ. Med. Coll., and PHYLLIS KRAFFT NEWILL. Pp. 269. New York: Doubleday, Doran & Co., 1944. Price, $2.50.

Taber's Dictionary of Gynecology and Obstetrics. By CLARENCE WILBUR TABER, Medical Editor and Author of Taber's Cyclopedic Medical Dictionary, Taber's Condensed Medical Dictionary, and Dictionary of Food and Nutrition, etc. With the Collaboration of MARIO A. CASTALLO, M.D., F.A.C.S., Assistant Professor of Obstetrics, Jefferson Med. Coll.; Gynecologist to St. Mary's and St. Agnes' Hosp.; Obstetrician to St. Mary's Hosp.; Diplomate, American Board of Obstetrics and Gynecology, etc., etc. Pp. 706; numerous illus. Philadelphia: F. A. Davis, 1944. Price, $3.50.

Proteins and Amino Acids. Physiology, Pathology, Therapeutics. By The Scientific Staff of the Arlington Chemical Company. Pp. 189. New York: Arlington Chemical Co., 1944.

Virus Diseases in Man, Animal and Plant. By GUSTAV SEIFFERT. A Survey and Reports Covering the Major Research Work Done During the Last Decade. Pp. 332. New York: Philosophical Library, 1944. Price, $5.00.

The British Encyclopædia of Medical Practice Including Medicine, Surgery, Obstetrics, Gynæcology and Other Special Subjects. Cumulative Supplement, 1944. Under the General Editorship of SIR HUMPHREY ROLLESTON, BT., G.C.V.O., K.C.B., M.D., D.Sc., F.R.C.S., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge; Sometime President of The Royal Coll. of Physicians of London. Pp. 306. London: Butterworth & Co., 1944.

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The British Encyclopædia of Medical Practice Including Medicine, Surgery, Obstetrics, Gynæcology and Other Special Subjects. Medical Progress, 1944. Under the General Editorship of SIR HUMPHREY ROLLESTON, BT., G.C.V.O., K.C.B., M.D., D.Sc., F.R.C.S., D.C.L., LL.D., Emeritus Regius Professor of Physics, Cambridge; Sometime President of The Royal Coll. of Physicians of London. Pp. 537. London: Butterworth & Co., 1944.

NEW EDITIONS

Physiology in Health and Disease. By CARL J. WIGGERS, M.D., D.Sc., F.A.C.P., Professor of Physiology and Director of Physiology Dept. in the School of Med. of Western Reserve Univ., Cleveland, Ohio. Fourth Ed. Pp. 1174; 274 figs. Philadelphia: Lea & Febiger, 1944. Price, $10.00.

A Method of Anatomy. Descriptive and Deductive. By J. C. BOILEAU GRANT, M.C., M.B., CH.B., F.R.C.S. (EDIN.), Professor of Anatomy in the Univ. of Toronto. Third Ed. Pp. 822; 729 figs. Baltimore: Williams & Wilkins, 1944. Price, $6.00.

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